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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

MEMORANDUM

Date: 02-MAR-2007

Subject: **Mesotrione**. Section 3 Request for Use on Berry Group 13, Cranberry, Flax, and Millet (PP#6F7023) and Section 18 Request for Emergency Exemption Use on Grain Sorghum (Reg#: 06KS01). Summary of Analytical Chemistry and Residue Data.

DP#s:	326898, 332812	Decision #s:	363609, 365010
PC Code:	122990	MRID #s:	46726301-46726307
40 CFR 180.	571		
Chemical Class:	Triketone herbicide (Group 27)		

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This document was originally prepared under contract by Dynamac Corporation (2275 Research Blvd. Suite 300; Rockville, MD 20850; submitted 29-SEP-2006). The document has been reviewed by the Health Effects Division (HED) and revised to reflect current Office of Pesticide Programs (OPP) policies.

Executive Summary

Mesotrione (2-[4-(methylsulfonyl)-2-nitrobenzoyl]-1,3-cyclohexanedione; designated by the company code ZA1296) is a triketone herbicide which inhibits the enzyme *p*-hydroxyphenyl-pyruvate dioxygenase (HPPD), disrupting carotenoid biosynthesis. This process leads to the destruction of chlorophyll, resulting in a bleaching effect in susceptible plants. Mesotrione is intended for pre-emergence and postemergence use for selective control of annual broadleaf weeds. Mesotrione is currently registered for use on field, pop, and sweet corn, and Section 18 Emergency Exemption Use on cranberry (set to expire 31-DEC-2007). There are also Special Local Need (SLN) uses approved in Illinois and Minnesota for the oilseed crop, cuphea.

Syngenta Crop Protection, Inc., has submitted a petition for the establishment of permanent tolerances for residues of the herbicide mesotrione on the berry group, cranberry, flax, and millet. The petitioner is proposing the establishment of permanent tolerances for residues of mesotrione in/on the following commodities:

Flax, seed	0.01 ppm
Flax, meal	0.01 ppm
Millet, grain	0.01 ppm
Millet, forage	0.01 ppm
Millet, hay	0.02 ppm
Millet, straw	0.02 ppm
Berry group	0.01 ppm
Cranberry	0.01 ppm

Concurrently, Syngenta has proposed to amend the product label for the 4 pounds per gallon (lb/gal) flowable-concentrate (FlC) formulation of mesotrione (Callisto® Herbicide; EPA Reg. No. 100-1131) to add uses on selected berries, cranberry, flax, and millet. The 4 lb/gal FlC formulation is to be applied to selected berries as up to two prebloom directed applications or to nonbearing low bush blueberries as up to two foliar broadcast applications at maximum seasonal rates of 0.188 lb active ingredient per acre (ai/A), to cranberries as up to two foliar applications made prior to fruit set at a maximum seasonal rate of 0.50 lb ai/A, and to flax and millet as a single pre-emergence application at 0.188 lb ai/A. Label revision and/or clarification are required concerning the use of crop-oil concentrate (COC) when Callisto® is applied to the above crops.

Furthermore, the Kansas (KS) Department of Agriculture has proposed a Section 18 Emergency Exemption for the use of mesotrione on grain sorghum to control weeds that are resistant to atrazine and herbicides which inhibit acetolactate synthase (ALS). This is the first year for a request for this use. The KS Department of Agriculture has requested the use of Lumax™ Herbicide (EPA Reg.#: 100-1152; contains 2.94% ai; other ai's in the product are S-metolachlor and atrazine) for grain sorghum. Applications under the proposed exemption will start 2 weeks prior to the start of sorghum planting. Lumax™ may only be applied pre-emergent, 7-14 days before planting at a one-time application rate of 0.168 lb ai/A using ground equipment only.

Tolerances for residues of mesotrione are currently established for field corn forage, grain, and stover, popcorn grain and stover, and sweet corn forage, kernel plus cob with husks removed, and stover. Tolerances for sweet corn forage and stover are established at 0.5 and 1.5 ppm,

respectively, and all remaining tolerances are established at 0.01 ppm [§180.571(a)]. A Section 18 Emergency Exemption time-limited tolerance, which expires 12/31/07, is established for residues of mesotrione in/on cranberry at 0.01 ppm [§180.571(b)]. If a permanent tolerance on cranberry is granted by RD, then the time-limited tolerance should be removed. Section 18 tolerances are still listed for sweet corn commodities; these tolerances expired 03-JUN-2004 and should be removed.

The submitted peanut metabolism data are acceptable; however, the submitted cranberry metabolism data are inadequate because no data were submitted reflecting application of mesotrione labeled in the cyclohexane ring to cranberries. For purposes of this petition, HED will not require additional metabolism data for cranberry for the following reasons: (1) the metabolism of PH-labeled mesotrione was similar in cranberry, peanut, and corn, suggesting that the metabolic routes for mesotrione are similar in all three crops; (2) results from corn and peanut metabolism studies reflecting application of CY-labeled mesotrione indicate that additional residues of concern are unlikely to be found following application of CY-labeled mesotrione to cranberries; and (3) results from the submitted crop field trials for cranberry (refer to 46726307.der.doc) and bush and cane berries (refer to 46726301.der.doc) indicate that residues of mesotrione were below the LOQ in/on all samples following treatment according to the proposed use patterns.

HED notes that, because the petitioner did not conduct a cranberry metabolism study reflecting CY-labeling, the requirement to demonstrate that metabolism of mesotrione is similar in three dissimilar crops has not been completely fulfilled. Therefore, additional plant metabolism data may be required to support future uses on additional crops.

The qualitative nature of the residue in *livestock* is adequately understood based on acceptable, previously reviewed, studies in cattle and hen. The qualitative nature of the residue in *plants* is adequately understood for the purposes of these petitions based on acceptable field corn and the cranberry and peanut metabolism studies submitted in support of these actions. The results of plant metabolism studies reflecting application of mesotrione labeled in the phenyl ring indicate that the major metabolic pathway in corn, cranberry, and peanut involves cleavage of the cyclohexanedione ring to yield MNBA, which is further reduced to its amino analog, AMBA. Mesotrione may also undergo hydroxylation to form 4-OH-mesotrione. The results of metabolism studies reflecting application of mesotrione labeled in the cyclohexanedione ring (corn and peanut only) show that the cyclohexanedione ring may be degraded to CO_2 which is incorporated into natural products, and the cyclohexanedione ring may be oxidized to form 4-OH-mesotrione which is further metabolized to form multiple metabolites. With the exception of 4-OH-mesotrione, metabolites containing both ring moieties were not characterized in any metabolism study. A cranberry metabolism study reflecting labeling in the cyclohexanedione ring will not be required to support the current action.

The HED MARC previously concluded that the residue of concern in field corn and livestock commodities is mesotrione *per se* (Memo, S. Levy, 26-APR-2001; DP#: 274111). For purposes of these petitions, the risk assessment team concluded that mesotrione *per se* is the residue of concern for tolerance enforcement and risk assessment purposes in berries, cranberries, flax, and millet for the following reasons: parent was the major residue identified in the cranberry metabolism study accounting for 60.2-67.1%TRR; although the metabolite AMBA was also a significant component of the TRR, it accounted for only approximately half the level found of parent; the HED MARC previously concluded that AMBA is less toxic that the parent; and since residues of parent in the cranberry field trial are <LOQ, residues of AMBA are expected to be non-quantifiable.

The qualitative nature of the residue in rotational crops is adequately understood based on acceptable confined rotational crop study. The HED MARC previously concluded that for tolerance expression and risk assessment purposes, the residue of concern in/on rotational crops is mesotrione *per se* (Memo, S. Levy, 26-APR-2001; DP#: 274111). Based on the results of a previously reviewed limited field rotational crop study, the following PBIs proposed on the label for Callisto® Herbicide are adequate: (i) 120 days for small grains; (ii) 10 months for soybeans, sorghum, cotton, peanuts, potatoes, sunflowers, canola, tobacco, and alfalfa; and (iii) 18 months for sugar beets, peas, dry beans, snap beans, cucurbits, red clover, and all other rotational crops.

A high-performance liquid chromatography (HPLC)/fluorescence detector (FLD) enforcement method, method TMR0882B, is available for the enforcement of tolerances in plant commodities. The method was reviewed and subjected to a successful petition method validation (PMV) under the previous petition for use on field corn (PP#8F04954). Samples from the submitted bush and cane berry, cranberry, flax and millet field trials were analyzed using an acceptable liquid chromatography (LC)/mass spectrometry (MS)/MS method, method RAM 366/01, that was previously submitted and reviewed as a confirmatory enforcement method. The limits of quantitation (LOQs) ranged from 0.01 to 0.015 ppm.

There are adequate storage stability data to support the storage conditions and intervals of samples from the cranberry field trials, and available storage stability data for corn and soybean matrices are adequate to support the storage intervals and conditions of samples from the flax and millet field trials. **Supporting storage stability data for berries remain outstanding.**

Adequate field trial data are available for cranberries, flax, and millet; additional storage stability data are required to support the berry field trials. Provided the petitioner amends the proposed label by removing recommendations for use of a spray adjuvant for applications to flax and millet, or provides evidence that a surfactant was used in the spray mixtures in the submitted crop field trials, the available field trial data will support tolerances for residues of mesotrione *per se* in/on flax seed, and millet grain and forage at 0.01 ppm and in/on cranberry and millet straw and hay at 0.02 ppm. Pending submission of the outstanding storage stability data, and provided the petitioner amends the proposed label by removing recommendations for use of a spray adjuvant for applications to berry, group 13, or provides evidence that a surfactant was used in the spray mixtures in the submitted crop field trials, the berry field trial data will support a tolerance for berry, group 13 at 0.01 ppm. HED notes that, pending revisions to the berry crop group, a separate tolerance should be established for lingonberry (Memo, B. Schneider, 14-JUN-2002; No DP#).

There are no available mesotrione field trial data for grain sorghum. The established tolerances for residues of mesotrione *per se* in/on corn commodities are appropriate for translation for this Section 18 request on grain sorghum; therefore, HED recommends the following time-limited tolerances: sorghum, grain, grain at 0.01 ppm; sorghum, grain, forage at 0.50 ppm; and sorghum, grain, stover at 1.5 ppm.

The submitted flax seed processing data are adequate, and indicate that residues of mesotrione do not concentrate in flax meal. These data indicate that the proposed tolerance for flax meal is not required. There are no processed commodities for grain sorghum that require tolerances at this time.

No feeding study data have been submitted for mesotrione. HED previously concluded that there was no reasonable expectation of quantifiable mesotrione residues of concern in eggs, milk, and the meat, fat, or meat byproducts of poultry and ruminants as a result of the registered uses on field and sweet corn. The only crops with associated livestock feed items under the Section 3 petition are flax (meal) and millet (grain, forage, hay, and straw). Although the proposed use on flax results in a slight increase in the dietary burden to poultry and hog, there is no expectation of finite residues in livestock commodities from the proposed uses on flax and millet. For purposes of this Section 18 registration only, the corn residue data will be translated to grain sorghum; therefore, grain sorghum feed commodities are not included in the dietary burden. Translation of the corn data to grain sorghum results in eliminating sorghum from the dietary burden calculation since the residues and the percents in diet are the same; therefore, inclusion of grain sorghum is unnecessary.

Regulatory Recommendations and Residue Chemistry Deficiencies

Provided a revised Section B and a revised Section F are submitted, there are no residue chemistry requirements that would preclude granting an unconditional registration for the requested Section 3 uses of mesotrione on cranberry, flax, and millet, and granting a conditional registration for use on the berry group pending submission of the outstanding storage stability data. HED recommends the following permanent tolerances:

Flax, seed	0.01 ppm
Millet, grain	0.01 ppm
Millet, forage	0.01 ppm
Millet, hay	0.02 ppm
Millet, straw	0.02 ppm
Berry, group 13	0.01 ppm
Lingonberry	0.01 ppm
Cranberry	0.02 ppm

For purposes of this Section 18 registration only, the corn residue data will be translated to grain sorghum; therefore, HED recommends the following time-limited tolerances:

Sorghum, grain, grain	0.01 ppm
Sorghum, grain, forage	0.50 ppm
Sorghum, grain, stover	1.5 ppm

A human-health risk assessment will be prepared in a separate document.

860.1200 Directions for Use

- The petitioner should either amend the proposed label by removing recommendations for use of a spray adjuvant for applications to berries, flax, and millet, or provide evidence that a surfactant was used in the spray mixtures in the submitted crop field trials.

- If the information concerning equipment type and spray volumes appearing under the general "Directions for Use and Application Procedures" section apply to berries, group 13, cranberries, flax, and/or millet, this should be clearly indicated on the product label. Otherwise, the label should be revised to include this information for the subject crops.

860.1380 Storage Stability

- Storage stability data are required to support the storage intervals and conditions of samples from the berry field trials.

860.1550 Proposed Tolerances

- The petitioner should submit a revised Section F reflecting the HED-recommended tolerance of 0.02 ppm for cranberry.
- The proposed tolerance for "berry group" should be revised to reflect the correct commodity definition: "Berry, group 13" and "lingonberry".

Background

The chemical structure and nomenclature of mesotrione is presented in Table 1. The physicochemical properties of the technical grade of mesotrione are presented in Table 2.

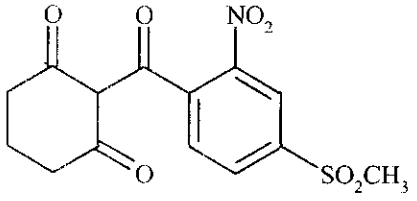
Table 1. Mesotrione Nomenclature.	
Chemical structure	
Common name	Mesotrione
Company experimental name	ZA1296
IUPAC name	2-(4-mesyl-2-nitrobenzoyl)cyclohexane-1,3-dione
CAS name	2-[4-(methylsulfonyl)-2-nitrobenzoyl]-1,3-cyclohexanedione
CAS registry number	104206-82-8
End-use product (EP)	4 lb/gal FlC (Callisto® Herbicide; EPA Reg. No. 100-1131)

Table 2. Physicochemical Properties of Mesotrione.		
Parameter	Value	Reference
Melting range	148.7-152.5°C	RD Memo, H. Podall, 24-FEB-2000; DP#: 263245
pH	3.4 (1% dispersion in water; 25°C)	
Density	1.46 g/mL, 20°C	
Water solubility	20°C 160 ppm, unbuffered water 0.22 g/100 mL, pH 4.8 1.5 g/100mL, pH 6.9 2.2 g/100 mL, pH 9	
Solvent solubility	20°C 0.37 g/100 mL, methanol 1.7 g/100 mL, ethyl acetate 0.27 g/100 mL, toluene 10.4 g/100 mL, acetonitrile <0.03 g/100 mL, heptane 8.1 g/100 mL, acetone	
Vapor pressure	4.3 x 10^{-8} torr, 20°C	
Dissociation constant, pK_a	3.12, 20°C	
Octanol/water partition coefficient, Log(K_{OW})	20°C log P_{OW} = 0.11 in unbuffered water log P_{OW} = 0.90 in pH 5 buffer log P_{OW} <-1 at pH 7 and 9 buffered water	
UV/visible absorption spectrum	Absorption maximum in methanol at 256 mu, with a molar extinction coefficient of 2.24 x 104 M cm.	

860.1200 Directions for Use

Syngenta has submitted a proposed label for the 4 lb/gal FlC formulation (Callisto® Herbicide; EPA Reg. No. 100-1131) and the KS Department of Agriculture has proposed use of a registered label (Lumax™; EPA Reg. No. 100-1152) for use on sorghum. The proposed Section 3 use directions for berries, cranberry, flax, and millet and the proposed Section 18 use directions for sorghum are presented in Table 3.

Table 3. Summary of Directions for Use of Mesotrione.

Applic. Timing, Type, and Equip.	Formulation [EPA Reg. No.]	Applic. Rate (lb ai/A)	Max. No. Applic. per Season	Max. Seasonal Applic. Rate (lb ai/A)	PHI (days)	Use Directions and Limitations
Bush and Cane Berries (Crop Subgroup 13B) [*sic.*][1] including bearing high bush blueberry, lingonberry, black and red raspberry, and blackberry, and nonbearing low bush blueberries						
Pre-bloom, directed [equipment not specified]	4 lb/gal EC [100-1131]	0.094-0.188 (split = 0.094 + 0.094)	2	0.188	Not specified (NS)	Applications are to be made to bearing high bush blueberry, lingonberry, black and red raspberry, and blackberry. A minimum 14-day retreatment interval (RTI) is specified. Use of a COC at 1% v:v is recommended. Application to bush or cane berries after onset of the bloom stage is prohibited.
Foliar, broadcast [equipment not specified]	4 lb/gal EC [100-1131]	0.094-0.188 (split = 0.094 + 0.094)	2	0.188	NS	Applications are to be made to low bush blueberry in the nonbearing year. A minimum 14-day RTI is specified. Use of a COC at 1% v:v is recommended.

Cranberry (bearing or nonbearing)						
Foliar [type and equipment not specified]	4 lb/gal EC [100-1131]	0.25	2	0.50	45	In bearing cranberries, applications are to be made after bud break but before fruit set and ≥45 days prior to flooding or harvest; in nonbearing cranberries, applications are to be made after bud break but ≥45 days prior to flooding. A minimum 14-day RTI is specified. Use of a COC at 1% v:v is recommended. Application directly to water or through any type of irrigation system is prohibited.

Flax						
Pre-emergence [type and equipment not specified]	4 lb/gal EC [100-1131]	0.188	1	0.188	NS	If weeds are emerged at application, use of a COC at 1% v:v is recommended. A UAN (urea + ammonium nitrate) fertilizer at 2.5% v:v or AMS (ammonium sulfate) fertilizer at 8.5 lb/100 gal spray solution may be added to improve burndown of existing weeds.
Millet						
Pre-emergence [type and equipment not specified]	4 lb/gal EC [100-1131]	0.188	1	0.188	NS	If weeds are emerged at application, use of a COC at 1% v:v is recommended. A UAN fertilizer at 2.5% vv or AMS fertilizer at 8.5 lb/100 gal spray solution may be added to improve burndown of existing weeds.
Section 18: Grain Sorghum						
Pre-emergence. 7-14 days pre-plant. Broadcast non-incorporated application using ground application only.	2.94% Liquid [100-1152]	0.168	1	0.168	60	Total acreage to be treated: 150,000 A. Total amount of pesticide that may be used: 25,125 lbs ai/A. Do not use aerial equipment or irrigation system. Do not apply to emerged grain sorghum, or in the production of forage sorghum, sudangrass, sorghum-sudangrass hybrids, or dual purpose sorghum.

[1] The label states that not all cultivars and types of berries that are included in the EPA definition of bush and cane berries (Crop Subgroup 13B) have been tested and shown to have adequate crop safety to Callisto herbicide. Those that have been tested and are believed to be reasonably fit are listed. Note that the petitioner should change the use on the label to "Berry, group 13".

Section 3: HED notes that the proposed Section 3 label is a full label which also reflects registered uses for field, pop, and sweet corn. The label sections reflecting established uses are identical to the currently accepted label (acceptance date 09-FEB-2006) except for minor changes to the rotational crop restrictions (detailed below). In the introduction to the directions for use for berries, cranberry, flax, and millet, the label states the following: ". . . specific directions for the use of Callisto® in these crops are provided below. These crops can have application rates, timings and methods, and/or precautions and restrictions that are very different than those for the use of Callisto® in registered corn crops."

The type of spray equipment and the spray volumes to be used was not specified for any of the crops for which use is proposed under the current action; however, under the general 'Directions for Use' section, the label states that aerial application is not to be used unless there is valid Supplemental Labeling bearing directions for use for aerial application. In addition, under Application Procedures, the label states that postemergence applications using ground equipment are to be made using spray volumes of 10-30 gal/A, and pre-emergence applications using ground equipment are to be made using spray volumes of 10-80 gal/A using water or liquid fertilizer (excluding suspension fertilizers) as the carrier.

The following rotational crop restrictions are specified under the 'General Directions for Use' section on the label: Corn (all types) may be replanted immediately. Small grains may be replanted 120 days after application. Soybeans, sorghum, cotton, peanuts, potatoes, sunflowers, canola, tobacco, and alfalfa can be planted back the following season but not less than 10 months after the last application. Sugar beets, peas, dry beans, snap beans, cucurbits, red clover, and all other rotational crops may be replanted 18 months after application. HED notes that these restrictions differ from those appearing on the currently accepted label in that sugar cane was removed from the list of crops that can be planted 120 days after the last application, and flax and grasses grown from seed were removed from the list of crops that can be planted 10 months after the last application, respectively.

Under the specific use directions for bush and cane berries and cranberries, the label specifies that there is an 18-month PBI for replanting bush or cane berries, cranberries, or rotating to another crop. Under the specific use directions for flax and millet, the label refers to the rotational crops restrictions for corn (*i.e.*, those appearing under Directions for Use).

Section 18: The KS Department of Agriculture has requested the use of Lumax™ Herbicide (EPA Reg.#: 100-1152; contains 2.94% ai; other ais in the product are S-metolachlor and atrazine) for grain sorghum. Applications under the proposed exemption will start 2 weeks prior to the start of sorghum planting. All applicable restrictions, precautions, and use requirements printed on the registered Lumax™ Herbicide product label must be followed, as well as those on the Section 18 Supplemental Label. Lumax™ may not be applied to emerged grain sorghum. It is not to be used in the production of grain sorghum grown on coarse textured soils such as sands, loamy sands, or sandy loams.

Conclusions

Section 3: The submitted crop field trial data for berries, flax, and millet do not support the proposed use directions because the proposed label states that use of a COC is recommended, and, based on the information contained in MRIDs 46726301 (berries), 46726303 (flax), and 46726302 (millet), no adjuvant was used in the field trials for berries and flax, and a nonionic surfactant and a COC were used in one trial each for millet. The petitioner should either amend the proposed label by removing recommendations for use of a spray adjuvant for applications to berries, flax, and millet, or provide evidence that a surfactant was used in the spray mixtures in the submitted crop field trials.

The type of spray equipment to be used and the spray volumes were not specified for any of the crops for which use was proposed. If the information concerning equipment type and spray volumes appearing under the general Directions for Use and Application Procedures apply to berries, group 13, cranberries, flax, and/or millet, this should be clearly indicated on the product label. Otherwise, the label should be revised to include this information for the subject crops.

HED notes that the use directions for berries appear under the heading "Bush and Cane Berries (Crop Subgroup 13B)"; however, the berries listed include berries that are not included in subgroup 13B. Therefore, the petitioner should change the heading to "Berries, Group 13".

Section 18: The Section 18 Supplemental Label is adequate.

860.1300 Nature of the Residue – Plants/Livestock

DER Reference: 46726306.der.doc (Cranberry)
46726304.der.doc (Peanut; includes review of MRID 46726305)
Memo, S. Levy, 26-APR-2001; DP#: 274111
Memo, S. Levy, 06-JUN-2001; DP#: 245477
Memo, W. Cutchin, 12-JAN-2005; DP#: 283827

New plant metabolism studies on cranberry and peanut were submitted with the current petition reflecting ^{14}C-labeling in the cyclohexane (CY) and/or phenyl (PH) rings of mesotrione. In addition, field corn metabolism studies, reflecting CY- and PH-labeling were previously submitted in conjunction with the petition for field corn uses (PP#8F04954). No new livestock metabolism studies were submitted with the current petition. Cattle and hen metabolism studies, reflecting labeling in the CY- and PH-rings of mesotrione, were previously submitted in conjunction with the petition for field corn uses (PP#8F04954).

Corn

In the available field corn metabolism studies, reflecting pre-emergence or postemergence application, mesotrione was identified at low levels (0.4-3.0% total radioactive residues (TRR)) in corn forage, indicating that residues were metabolized. Metabolite 4-OH-mesotrione was identified in forage and stover from the PH-label studies, and in forage from the CY-label studies at low levels (6.1-10.4% TRR). Metabolites 4-OGlu ZA1296, MNBA and AMBA were only identified in corn matrices from the PH studies; AMBA (free, acid-labile, base-labile, and hexose esters) metabolite levels were greater following postemergence treatment than pre-emergence

treatment. Metabolite 4-OGlu ZA1296 was identified in forage from the PH studies at low levels (3.6-3.8% TRR). AMBA was the major metabolite identified in forage (12.2-13.2% TRR) and stover (13.6-28.2% TRR) from the PH studies. MNBA was also identified in PH forage (3.4-19.7% TRR) and stover (1.0-1.9% TRR). A large amount of residues were characterized as minor compounds with diverse polarity. Based on mobility and responses to hydrolysis, the unknown polar components in the PH studies, were considered to be similar to 4-OGlu ZA1296 and were likely polar conjugates, with endocons of neutral or amphoteric character. In the CY-label studies, the incorporation of radioactivity into carbohydrates, such as glucose, fructose, and malic acid, was demonstrated. The incorporation of radioactivity into lignin and cellulose was also characterized in postemergence stover.

The metabolite profiles differed significantly in the PH and CY studies. Little of the residue characterized from the PH studies resulted from the fixation of ^{14}C, while the identification of carbohydrates in the CY studies indicated that incorporation of ^{14}C into biomolecules was the major source of radioactive residues.

In an additional study reflecting pre-emergence plus postemergence applications, residues of the parent, mesotrione, were not detected. Metabolite 4-OH-mesotrione was identified only in corn forage at low levels (5.4% TRR). AMBA, MNBA, and their conjugates were identified in both forage (2.2-4.6% TRR) and stover (1.0-2.3% TRR). As was observed in the separate pre-emergence and postemergence studies, minor compounds represented the largest amount of the radioactivity; however, each of these components was individually present at <0.01 ppm.

Cranberry

Syngenta Crop Protection, Inc. has submitted a study investigating the metabolism of [phenyl-U-^{14}C]mesotrione (PH label; specific activity 40.8 µCi/mg for low-rate applications and 21.1 µCi/mg for high-rate applications) in cranberries. The radiolabeled test substances were formulated as emulsifiable-concentration (EC) formulations and applied as two broadcast foliar applications to cranberries 33 and 49 days post-transplant at 0.30 and 0.22 lb ai/A for a total application rate of 0.52 lb ai/A (low rate; ~1x), or 0.82 and 0.57 lb ai/A for a total application rate of 1.39 lb ai/A (high rate; ~2.8x). Samples of cranberries and foliage were collected at maturity, 46 days after the last application.

TRR were 2.573 ppm in cranberries and 16.832 ppm in foliage collected 46 days following the low-rate application, and 4.853 ppm in cranberries and 31.804 ppm in foliage collected 46 days following the high-rate application. Only cranberries were subjected to analysis for residue characterization and identification.

Solvent extraction with acetonitrile (ACN)/water released a reported ~103% TRR in low-rate cranberries and ~102% TRR in high-rate cranberries. Nonextractable residues accounted for 2.5% TRR (0.064 ppm) in low-rate cranberries and 2.2% TRR (0.107 ppm) in high-rate cranberries. Accountabilities were 104-105%. The extraction procedures were adequate. Residues were identified and quantitated by HPLC, and identification of metabolites was confirmed by thin-layer chromatography (TLC) co-chromatography and by LC/MS/MS (mesotrione only). Adequate storage stability data were submitted to support the storage intervals and conditions of samples from the study.

Mesotrione was the major residue identified in cranberries, accounting for 60.2% TRR (1.548 ppm) in low-rate cranberries and for 67.1% TRR (3.257 ppm) in high-rate cranberries. The metabolite AMBA, identified after peak isolation and acid hydrolysis, was also a significant component, accounting for 34.8% TRR (0.895 ppm) in low-rate cranberries and for 24.3% TRR (1.178 ppm) in high-rate cranberries. Metabolite MNBA was identified at 3.0% and 1.6% TRR (0.076 and 0.078 ppm) in low- and high-rate cranberries, respectively. Remaining radioactivity was simply characterized as "baseline" and accounted for ≤2.5% TRR.

Based on the cranberry metabolism study, the major metabolic pathway in cranberries involves cleavage of the cyclohexanedione ring to yield MNBA, which is further reduced to its amino analog, AMBA. HED notes that the proposed pathway is similar to that observed in field corn following treatment with PH-labeled mesotrione (Memo, S. Levy, 06-JUN-2001; DP#: 245477).

Peanut

Syngenta Crop Protection, Inc. has submitted two studies investigating the metabolism of [cyclohexane-2-^{14}C]mesotrione (CY label; specific activity 40.1 µCi/mg) and [phenyl-U-^{14}C]mesotrione (PH label; specific activity 40.5 µCi/mg) in peanuts. In separate studies, the radiolabeled test substances were formulated and applied as a single pre-emergence application one day after planting peanut seed at nominal rates of 0.29 lb ai/A (327 g ai/ha) and 0.75 lb ai/A (836 g ai/ha) for the CY label, and 0.27 lb ai/A (305 g ai/ha) and 0.71 lb ai/A (796 g ai/ha) for the PH label. The petitioner reported minor phytotoxic effects in peanuts treated at the high rate for both labels. Samples of peanut foliage were collected at 50% mature harvest, 90 days after application, and samples of mature peanut hay and peanuts were collected 154 days after application. Peanuts were separated into hulls and nutmeat following harvest.

TRR in peanut matrices were determined by combustion/liquid-scintillation counting (LSC). Following application of CY-labeled mesotrione at 0.29 lb ai/A, TRR were 0.006 ppm in 50% mature foliage, 0.004 ppm in hay, and 0.005 and 0.007 ppm in hulls and nutmeat, respectively. Following application at 0.75 lb ai/A, TRR were 0.020 ppm in foliage, 0.011 ppm in hay, and 0.015 and 0.022 ppm in hulls and nutmeat, respectively. Following application of PH-labeled mesotrione at 0.27 lb ai/A, TRR were 0.028 ppm in 50% mature foliage, 0.012 ppm in hay, and 0.011 and 0.013 ppm in hulls and nutmeat, respectively. Following application at 0.71 lb ai/A, TRR were 0.064 ppm in foliage, 0.028 ppm in hay, and 0.025 and 0.037 ppm in hulls and nutmeat, respectively. In the CY-label study, only samples from the high rate were subjected to further extraction and analysis for characterization of residues.

In the CY-label study, solvent extraction with ACN/water released ~43%, 27%, and 20% TRR in 50% mature foliage, hay, and hulls respectively. No further attempts were made to release radioactivity from these matrices; nonextractable residues were 65.9-84.5% TRR (0.008-0.013 ppm). Nutmeats were subjected to two separate extraction procedures intended to resolve polar and nonpolar residues. In the first procedure, extraction with ACN/water and ethyl acetate released 43.5% TRR (0.012 ppm); in the second procedure, extraction with hexane and ethyl acetate released 51.4% TRR (0.011 ppm). Nonextractable residues in nutmeat, accounting for 50.8% TRR (~0.011 ppm), were not further investigated. Although nonextractable residues accounting for ≥50% TRR in all matrices were not further investigated, HED concludes that the extraction procedures were adequate because TRR were low in all peanut matrices, and metabolism of mesotrione appeared to be extensive. Residues were identified and quantitated by

HPLC following further characterization via anion-exchange chromatography or solid-phase extraction (SPE) on an amino column (for nutmeats).

In the PH-label study, solvent extraction with ACN/water released ~41-42%, 32-34%, and 20-23% TRR in low- and high-rate 50% mature foliage, hay, and hulls respectively. Additional radioactivity was released from the nonextractable residues by refluxing with water followed by acid and base hydrolysis. These procedures released ~27-52%, 41-42%, and 31-38% TRR in low- and high-rate foliage, hay, and hulls. Remaining nonextractable residues, accounting for 13%, 26%, and 46% TRR (0.003-0.005 ppm) in low-rate foliage, hay, and hulls and for 26%, 24%, and 20% TRR (0.005-0.016 ppm) in high-rate foliage, hay, and hulls, were characterized as cellulose or lignins on the basis of base and acid hydrolysis. For nutmeats, extraction with hexane released 36% and 32% TRR (0.005 and 0.012 ppm) in low- and high-rate samples, respectively. Additional radioactivity was released from the nonextractable residues by refluxing with water followed by acid and base hydrolysis. These procedures released ~92% TRR in low-rate nutmeats and ~29% TRR in high-rate nutmeats; remaining nonextractable residues, accounting for 16% TRR in low-rate nutmeats and 50% TRR (0.018 ppm) in high-rate nutmeats, were characterized as cellulose or lignin. The extraction procedures for the PH-label study were adequate. Residues were identified and quantitated by HPLC and identification of metabolites was confirmed by TLC co-chromatography.

Accountabilities, based on extraction procedures ranged 100-107% for the CY-label study. In the PH-label study, accountabilities ranged 92-114% for low- and high-rate foliage and hay, low-rate hulls, and high-rate nutmeats; accountabilities of 76% and 146% were obtained for high-rate hulls and low-rate nutmeats, respectively. The petitioner made no attempt to explain the low recovery observed for high-rate hulls or the excessively high recovery obtained for low-rate nutmeats, which resulted from high reported TRR in the aqueous and organic phases following dichloromethane (DCM) partitioning of the acidified hydrolysate of the nonextractable residues. HED furthermore notes, that the petitioner did not address the loss of radioactivity on further characterization/identification analysis following extraction procedures and did not provide quantitative data for minor unknowns for any fraction except the aqueous fraction following initial partitioning of the ACN/water phase.

Adequate storage stability data were submitted to support the storage intervals and conditions of raw agricultural commodities (RAC) samples and extracts from the CY- and PH-label studies.

Mesotrione was not identified in any peanut matrix following pre-emergence application of CY-labeled mesotrione at 0.75 lb ai/A. The only identified metabolite was 4-OH-mesotrione, at 1.6% (<0.001 ppm) and 1.4% (<0.001 ppm) TRR in 50% mature foliage and hay, respectively, and 0.5% (<0.001 ppm) TRR in hulls. Identification of this metabolite was adequately confirmed by LC/MS and a number of additional procedures. Minor unknowns (none present at ≥0.001 ppm in any matrix) accounted for 15.1% (0.003 ppm), 6.0% (0.001 ppm), and 3.3% (<0.001 ppm) TRR in foliage, hay, and hulls, and remaining radioactivity was characterized on the basis of anion-exchange chromatography (such as neutral/basic, neutral/acidic, or acidic) and distribution into organic solvents (including ACN, methanol, and ethanol) or aqueous phases. In peanut nutmeats, the distribution of polar residues was similar to that in the other matrices. Nonpolar residues in nutmeats were characterized as neutral lipids (37.8% TRR, 0.008 ppm), fatty acids (5.7% TRR, 0.001 ppm), and phospholipids (4.1% TRR, 0.001 ppm) on the basis of elution characteristics on amino SPE. The petitioner confirmed the presence of fatty acids via

additional characterization procedures using radiolabeled standards of glycerol and triacylglycerides labeled in the fatty acid portion of the molecule.

The metabolite profile following pre-emergence application of PH-labeled mesotrione differed from the profile observed in the CY-label study. Although mesotrione was not identified in any matrix from either treatment rate, metabolites MNBA (4-methanesulfonyl-2-nitro-benzoic acid) and AMBA (2-amino-4-methanesulfonyl-benzoic acid) were identified in all matrices, MBA was identified in foliage, hay, and nutmeat, and 4-OH-mesotrione was identified in nutmeat only. MNBA accounted for 12.4% TRR (0.003 ppm), 5.1% TRR (0.001 ppm), and 3.6% TRR (<0.001 ppm) in low-rate foliage, hay, and hulls, respectively, and was not identified in low-rate nutmeat.

In high-rate matrices, MNBA accounted for 11.1% TRR (0.007 ppm), 6.4% TRR (0.002 ppm), 9.6% TRR (0.002 ppm), and 2.4% TRR (0.001 ppm) in high-rate foliage, hay, hulls, and nutmeat, respectively. AMBA was identified in all matrices treated at low- and high-rates, respectively, at 16.7% and 7.1% TRR (0.005 ppm each) in foliage, 6.9% and 4.6% TRR (0.001 ppm each) in hay, 1.6% and 1.4% TRR (<0.001 ppm each) in hulls, and 15.0% and 1.4% TRR (0.002 and 0.001 ppm) in nutmeats. MBA was identified at 0.6% TRR (<0.001 ppm) in high-rate foliage, 3.2% and 2.8% TRR (<0.001 ppm each), respectively, in low- and high-rate hay, and at 6.7% TRR (0.001 ppm) in low-rate nutmeat. 4-OH-Mesotrione was identified in low-rate nutmeat at 6.9% TRR (0.001 ppm). Additional residues were characterized as cellulose and lignins on the basis of hydrolysis in all matrices as noted above, and, as in the CY-label studies, residues in low- and high-rate nutmeats were characterized as neutral lipids, fatty acids, and phospholipids on the basis of elution characteristics on amino SPE; the neutral lipid residues were further characterized on a second amino SPE column. Based on these analyses, residues in low- and high-rate nutmeats, respectively, were characterized as cholesterol esters (12.8% and 2.7% TRR), triacylglycerols (17.4% and 23.5% TRR), and monoacylglycerols (7.0% and 7.3% TRR), fatty acids (4.7% and 6.5% TRR), and phospholipids (7.0% TRR and trace). One major polar unknown, Peak 1, was found in all matrices from low- and high-rate treatments, respectively, at 17.6% and 11.2% TRR in foliage, 13.1% and 32.1% TRR in hay, 8.6% and 12.4% TRR in hulls, and 14.0% and 7.0% TRR in nutmeat. Peak 1 is believed to consist of AMBA conjugates. Discrete unknowns (identified on the basis of fraction collection by vial numbers) accounted for 1.9-11.4% TRR (≤0.003 ppm) in low- and high-rate foliage, hay, and hulls, and low-rate nutmeat, and minor unknowns (none present at ≥0.001 ppm in any matrix) accounted for at least 1.0-1.6% TRR in foliage, hay, and hulls from both rates. Remaining radioactivity was characterized on the basis of distribution into organic solvents (including ACN, methanol, and ethanol) or aqueous phases.

Based on the submitted CY-label metabolism study, the petitioner proposed that mesotrione is metabolized in peanuts by two pathways. In the first pathway, the cyclohexanedione ring is degraded to CO_2 which is incorporated into natural products, and in the second pathway, the cyclohexanedione ring is oxidized to form 4-OH-mesotrione which is further metabolized to form multiple metabolites. For PH-labeled mesotrione, metabolism proceeds via cleavage of the cyclohexanedione ring to yield MNBA. MNBA is reduced to its amino analog, AMBA, which is subsequently converted to numerous conjugates or further degraded to MBA. As was observed for the CY label, mesotrione may also undergo hydroxylation to form 4-OH-mesotrione. With the exception of 4-OH-mesotrione, metabolites containing both ring moieties were not characterized in either metabolism study. HED notes that these results are similar to those observed in field corn following treatment with CY- and PH-labeled mesotrione (Memo, S. Levy,

06-JUN-2001; DP#: 245477).

Cattle: In the cattle metabolism studies, [PH-^{14}C]mesotrione and [CY-2-^{14}C]mesotrione were each administered orally to a dairy cow for 7 consecutive days at respective feeding levels of 11.91 ppm and 9.9 ppm. The feeding levels corresponded to 25.8x and 22.6x the maximum theoretical dietary burden (MTDB; see Table 5) to beef and dairy cattle, respectively, for the PH label, and 21.5x and 18.8x the MTDB to beef and dairy cattle, respectively, for the CY label. In a separate study, [PH-^{14}C]AMBA was administered orally to a dairy cow for 7 consecutive days at a feeding level of ~10 ppm.

Hens: In the hen metabolism studies [PH-^{14}C]mesotrione and [CY-^{14}C]mesotrione were orally administered to a separate groups of laying hens for 10 consecutive days at feeding levels of ~10 ppm each (~1000x the maximum theoretical dietary burden to poultry; see Table 5).

Conclusions. The submitted peanut metabolism data are acceptable; however, the submitted cranberry metabolism data are inadequate because no data were submitted reflecting application of mesotrione labeled in the cyclohexane ring to cranberries. For purposes of this petition, HED will not require additional metabolism data for cranberry for the following reasons: (1) the metabolism of PH-labeled mesotrione was similar in cranberry, peanut, and corn, suggesting that the metabolic routes for mesotrione are similar in all three crops; (2) results from corn and peanut metabolism studies reflecting application of CY-labeled mesotrione indicate that additional residues of concern are unlikely to be found following application of CY-labeled mesotrione to cranberries; and (3) results from the submitted crop field trials for cranberry (refer to 46726307.der.doc) and bush and cane berries (refer to 46726301.der.doc) indicate that residues of mesotrione were below the LOQ in/on all samples following treatment according to the proposed use patterns.

HED notes that, because the petitioner did not conduct a cranberry metabolism study reflecting CY-labeling, the requirement to demonstrate that metabolism of mesotrione is similar in three dissimilar crops has not been completely fulfilled. Therefore, additional plant metabolism data may be required to support future uses on additional crops.

The qualitative nature of the residue in *livestock* is adequately understood based on acceptable, previously reviewed, studies in cattle and hen. The qualitative nature of the residue in *plants* is adequately understood for the purposes of these petitions based on acceptable field corn and the cranberry and peanut metabolism studies submitted in support of these actions. The results of plant metabolism studies reflecting application of mesotrione labeled in the phenyl ring indicate that the major metabolic pathway in corn, cranberry, and peanut involves cleavage of the cyclohexanedione ring to yield MNBA, which is further reduced to its amino analog, AMBA. Mesotrione may also undergo hydroxylation to form 4-OH-mesotrione. The results of metabolism studies reflecting application of mesotrione labeled in the cyclohexanedione ring (corn and peanut only) show that the cyclohexanedione ring may be degraded to CO_2 which is incorporated into natural products, and the cyclohexanedione ring may be oxidized to form 4-OH-mesotrione which is further metabolized to form multiple metabolites. With the exception of 4-OH-mesotrione, metabolites containing both ring moieties were not characterized in any metabolism study. A cranberry metabolism study reflecting labeling in the cyclohexanedione ring will not be required to support the current action.

The HED MARC previously concluded that the residue of concern in field corn and livestock commodities is mesotrione *per se* (Memo, S. Levy, 26-APR-2001; DP#: 274111). For purposes of these petitions, the risk assessment team concluded that mesotrione *per se* is the residue of concern for tolerance enforcement and risk assessment purposes in berries, cranberries, flax, and millet for the following reasons: parent was the major residue identified in the cranberry metabolism study accounting for 60.2-67.1%TRR; although the metabolite AMBA was also a significant component of the TRR, it accounted for only approximately half the level found of parent; the HED MARC previously concluded that AMBA is less toxic that the parent; and since residues of parent in the cranberry field trial are <LOQ, residues of AMBA are expected to be non-quantifiable.

860.1340 Residue Analytical Methods

DER Reference: None
Memo, J. Negron, 17-AUG-2001; DP#: 261112
Memo, S. Levy, 06-JUN-2001; DP#: 245477
Memo, W. Cutchin, 12-JAN-2005; DP#: 283827

Plant commodity methods

Enforcement method: The current enforcement method for plant commodities is an HPLC method with FLD, Method TMR0882B. This method was reviewed in conjunction with the field corn petition (PP#8F04954) and has undergone adequate PMV (Memo, J. Negron, 17-AUG-2001; DP# 261112).

An acceptable confirmatory method, LC/MS/MS method, RAM 366/01, was previously submitted and reviewed for the confirmation of residues of mesotrione and MNBA in corn commodities. The method is entitled "Residue Analytical Method for the Determination of Residues of Mesotrione and 4-(Methylsulfonyl)-2-Nitrobenzoic Acid (MNBA) in Crop Samples." The validated limit of quantitation (LOQ) was 0.01 ppm for each analyte in corn commodities. The limits of detection (LODs) were reported to be 0.002 ppm for mesotrione and 0.005 ppm for MNBA. This method has been forwarded to the U.S. Food and Drug Administration (FDA) for inclusion in the Pesticide Analytical Manual (PAM) Volume II as a confirmatory method. Validation by the EPA's Analytical Chemistry Laboratory (ACL) was not required.

Data collection method: Samples of berries, cranberries, flax, flax meal, and millet forage, hay, straw, and seed were analyzed for residues of mesotrione *per se* using modified versions of LC/MS/MS method RAM 366/01. The method is adequate for data collection based on acceptable method validation and/or concurrent recovery data for the listed matrices.

Minor modifications to the method were made for the analysis of cane and bush berries (*i.e.*, samples were not analyzed for MNBA, and the SPE cleanup step was omitted for some samples). Briefly, homogenized samples were mixed with sodium chloride (10:1, wt:wt) and extracted with ACN:water (1:1, v:v). An aliquot of the extract was diluted with formic acid, and cleaned up by SPE on a polymeric column; residues were eluted with methanol:formic acid (98:2, v:v). The eluate was evaporated to dryness, and residues were redissolved in 90% water/methanol for LC/MS/MS analysis. For some samples, the cleanup step was omitted; instead, an aliquot of the

ACN/water extract was diluted with water, and the final volume was adjusted with water/methanol for analysis. The monitored ion transition was m/z 338 → 291. The validated LOQ was 0.01 ppm, reflecting the lowest fortification with acceptable recoveries. The LOD, as determined by the smallest amount of analyte injected, was 0.001 ng.

Minor modifications to the method were made for the analysis of cranberry (*i.e.*, samples were not analyzed for MNBA; a methylene chloride partitioning step was added to remove pigments; and standards and samples were diluted with ACN/water to reflect the mobile phase). Briefly, homogenized samples were extracted with ACN:water containing 10 g/L sodium chloride (1:1, v:v) and centrifuged. An aliquot of the extract was diluted with water and formic acid, and cleaned up by SPE on a polymeric column; residues were eluted with methanol:formic acid (98:2, v:v). The eluate was diluted with water and partitioned into methylene chloride. The methylene chloride phase was evaporated to dryness, and residues were redissolved in ACN/water (10%, v:v) for LC/MS/MS analysis. The monitored ion transition was m/z 338 → 291. The lowest limit of method validation (LLMV) was 0.01 ppm. Based on recoveries at the LLMV, the calculated LOQ and LOD were 0.015 ppm and 0.005 ppm, respectively, for cranberry. HED notes that, although the petitioner used the LLMV of 0.01 ppm as the quantitation limit for reporting residue results, based on the calculated LOQ, the method does not reliably quantitate residues down to 0.01 ppm.

Minor modifications to the method were made for the analysis of flax seed and meal (*i.e.*, samples were not analyzed for MNBA, and the SPE cleanup step was omitted). Briefly, homogenized samples were mixed with sodium chloride (10:1, wt:wt) and extracted with ACN:water (1:1, v:v). An aliquot of the extract was diluted with water, and the final volume was adjusted with 90% water/methanol for LC/MS/MS analysis. The monitored ion transition was m/z 338 → 291. The validated LOQ was 0.01 ppm, reflecting the lowest fortification with acceptable recoveries. The LOD, as determined by the smallest amount of analyte injected, was 0.001 ng for flax seed and meal.

Minor modifications were made to the method for the analysis of millet matrices (*i.e.*, samples were not analyzed for MNBA, and the SPE cleanup step was omitted). Briefly, homogenized samples were mixed with sodium chloride (10:1, wt:wt) and extracted with ACN:water (1:1, v:v). An aliquot of the extract was diluted with water, and the final volume was adjusted with 90% water/methanol for LC/MS/MS analysis. The monitored ion transition was m/z 338 → 291. The validated LOQ was 0.01 ppm. The LOD, as determined by the smallest amount of analyte injected, was 0.001 ng for millet commodities.

Livestock commodity methods

Because no tolerances have been established or proposed for livestock commodities in conjunction with the registered and proposed uses of mesotrione, no livestock commodity methods have been submitted.

Conclusions. An acceptable HPLC/FLD enforcement method, method TMR0882B, is available for the enforcement of tolerances in plant commodities. Samples from the submitted bush and cane berry, cranberry, flax and millet field trials were analyzed using an acceptable LC/MS/MS method, method RAM 366/01, that was previously submitted and reviewed as a confirmatory enforcement method.

860.1360 Multiresidue Methods (MRM)

Memo, S. Levy, 16-NOV-1999; DP#: 260570

The petitioner submitted multiresidue method data with the previous petition, which were forwarded to FDA for full evaluation. The FDA PESTDATA database dated 06/05 (PAM Volume I, Appendix I) indicates that mesotrione is not recovered using MRM Sections 302 (Luke Method; Protocol D). No recovery data pertaining to MRM Section 303 (Mills, Onley, and Gaither Method; Protocol E, nonfatty food) or 304 (Mills Method; Protocol F, fatty food) were included. The MRM are not adequate for enforcement.

860.1380 Storage Stability

Memo, S. Levy, 06-JUN-2001; DP#: 245477

Storage stability data submitted with the previous petition for field corn uses, demonstrated that residues of mesotrione and its metabolite MNBA were relatively stable in/on various raw agricultural commodities stored under frozen conditions. Fortified residues of mesotrione and its metabolite MNBA were stable for up to 42 months in/on field corn forage, fodder, and grain, up to 44 months in/on radish root, and up to 40 months in/on soybean seed.

A concurrent storage stability study was conducted with the cranberry crop field trials. Although 0-day data were not provided, the storage stability data indicate that residues of mesotrione are relatively stable in/on fortified samples of cranberry stored frozen for up to 217 days.

The storage intervals and conditions of samples from the submitted cane and bush berry, cranberry, flax, and millet field trials and the flax processing study are reported in Table 4.

Table 4. Summary of Storage Conditions and Intervals of Samples from the Cane and Bush Berry, Cranberry, Flax, and Millet Field Trials and the Flax Processing Study.

Matrix	Storage Temperature (°C)	Actual Storage Duration	Interval of Demonstrated Storage Stability
Berries	~-15	95-501 days (3.1-16.4 months)	None available
Cranberry	<-10	230-238 days (7.6-7.8 months)	Residues of mesotrione are relatively stable in/on cranberry stored frozen for up to 217 days.
Flax, seed	~-15	292-382 days (9.6-12.6 months)	Residues of mesotrione are relatively stable in/on fortified soybean seed and corn matrices (forage, stover, and grain) stored frozen for 40-42 months.
Flax, seed	~-15	330 days (10.9 months)	Residues of mesotrione are relatively stable in/on fortified soybean seed and corn matrices (forage, stover, and grain) stored frozen for 40-42 months.
Flaxseed, meal	~-15	271 days (8.9 months)	None available; none required.
Millet, forage	~-15	300-414 days (9.9-13.6 months)	Residues of mesotrione are relatively stable in/on fortified soybean seed and corn matrices (forage, stover, and grain) stored frozen for 40-42 months.
Millet, hay		338-415 days (11.1-13.7 months)	
Millet, straw		297-351 days (9.8-11.5 months)	
Millet, grain		297-352 days (9.8-11.6 months)	

Conclusions. The concurrent storage stability data for cranberry, in conjunction with the available storage stability data for corn matrices, radish root, and soybean seed stored are adequate to support the storage conditions and intervals of samples from the submitted cranberry field trials. The available corn and soybean storage stability data will support the storage conditions and intervals of samples from the subject flax and millet field trials and RAC samples from the flax seed processing study. Because residues were nonquantifiable in the flax seed RAC following treatment at 5x the field trial rate, and a processing study would not typically have been required, HED will not require supporting storage stability data for the processed meal samples.

No storage stability data were submitted to support the storage intervals and conditions of samples from the berry field trials. The petitioner stated that the results of a storage stability study demonstrating the stability of mesotrione residues in/on berries stored frozen for 17 months will be submitted to the Agency upon completion. **Until receipt of the berry storage stability data, this requirement is considered a deficiency.**

860.1400 Water, Fish, and Irrigated Crops

There are no proposed uses that are relevant to this guideline topic.

860.1460 Food Handling

There are no proposed uses that are relevant to this guideline topic.

860.1480 Meat, Milk, Poultry, and Eggs

DER Reference: None
Memo, S. Levy, 26-APR-2001; DP#: 274111
Memo, W. Cutchin, 12-JAN-2005; DP#: 283827

No livestock feeding study data were submitted with this petition. In consideration of the MTDB to livestock based on field and sweet corn uses, HED previously concluded that there was no reasonable expectation of quantifiable mesotrione residues of concern in eggs, milk, and the meat, fat, or meat byproducts of poultry and ruminants as a result of the proposed uses [Category 180.6(a)(3)]. HED noted that, should a future proposed use significantly increase the calculated burden, a cattle feeding study may be required.

The crops with associated livestock feed items under the subject petitions are flax (meal), millet (grain, forage, hay, and straw), and sorghum (grain, forage, stover, and aspirated grain fractions). At the recommended tolerances, flax meal would contribute ≤0.001 ppm to the beef, dairy, and hog MTDB and 0.003 ppm to the hen MTDB. The anticipated contribution for millet matrices would be ≤0.008 for beef cattle, ≤0.020 ppm for dairy cattle, 0.007 ppm for poultry, and 0.008 ppm for hog. Because millet feed items fill the same dietary requirements as corn feed items, and because the dietary contribution of millet feed items is smaller than the corresponding dietary contribution for corn feed items, the proposed use on millet will not result in any significant change in the previously estimated MTDB. Addition of flax meal to the MTDB for hen and hog increases the estimated MTDB from 0.008 to 0.010 ppm for hen and from 0.008 to 0.009 ppm for hog.

For purposes of this Section 18 registration only, the corn residue data will be translated to grain sorghum; therefore, grain sorghum feed commodities are not included in the MTDB. Translation of the corn data to grain sorghum results in eliminating sorghum from the dietary burden calculation since the residues and the percents in diet are the same; therefore, inclusion of grain sorghum is unnecessary.

The MTDBs of mesotrione to livestock are presented in Table 5.

Table 5. Calculation of MTDB of Mesotrione to Livestock.				
Feedstuff	% Dry Matter[1]	% Diet[1]	Estimated Tolerance (ppm)	Dietary Contribution (ppm)[2]
Beef Cattle				
Sweet corn stover	83	25	1.5	0.452
Field corn grain	88	75	0.01	0.009
TOTAL BURDEN	--	100	--	**0.461**
Dairy Cattle				
Sweet corn forage	48	50	0.50	0.521
Field corn grain	88	40	0.01	0.005
TOTAL BURDEN	--	90[3]	--	**0.526**
Poultry				
Field corn grain	--	80	0.01	0.008
Flax meal	--	20	0.01	0.002
TOTAL BURDEN	--	100	--	**0.010**
Hog				
Field corn grain	--	80	0.01	0.008
Flax meal	--	10	0.01	0.001
TOTAL BURDEN	--	90[3]	--	**0.0090**

[1] Table 1 (OPPTS Guideline 860.1000).
[2] Contribution = ([tolerance /% DM] x % diet) for beef and dairy cattle; Contribution = (tolerance x % diet) for poultry and hog.
[3] The remainder of the diet will be composed of feedstuff derived from crops that do not have existing or proposed mesotrione uses

The proposed use on flax results in a slight increase in the MTDB to poultry, from 0.008 to 0.010 ppm. The maximum residues of mesotrione observed in the poultry metabolism studies were 1.097 ppm in liver. Based on the dosing levels, which were 1000x the revised estimated MTDB, the maximum expected residues of mesotrione in poultry commodities would be 0.001 ppm.

Conclusions. Although the proposed use on flax results in a slight increase in the dietary burden to poultry and hog, HED concludes that there is no expectation of finite residues in livestock commodities for the proposed uses on flax and millet. Should a future proposed use significantly increase the calculated burden, livestock feeding studies may be required.

860.1500 Crop Field Trials

DER References: 46726301.der.doc (berry group 13)
43726307.der.doc (cranberry)
46726303.de1.doc (flax)
46726302.der.doc (millet)

Table 6. Summary of Residue Data from Crop Field Trials with Mesotrione.

Crop matrix	Total Applic. Rate (lb ai/A)	PHI (days)	Residue Levels (ppm)						
			n	Min.	Max.	HAFT[1]	Median	Mean	Std. Dev.
BERRY, GROUP 13 (proposed use = 0.188 lb ai/A total application rate, PHI not specified)[2]									
Blueberry	0.091-0.098	32-88	12	<0.01	<0.01	<0.01	0.005	0.005	0.0
	0.186-0.193	32-88	12	<0.01	<0.01	<0.01	0.005	0.005	0.0
Raspberry	0.094-0.097	52-83	6	<0.01	<0.01	<0.01	0.005	0.005	0.0
	0.185-0.189	52-83	6	<0.01	<0.01	<0.01	0.005	0.005	0.0
Blackberry	0.096	62	2	<0.01	<0.01	<0.01	0.005	0.005	0.0
	0.195	62	2	<0.01	<0.01	<0.01	0.005	0.005	0.0
CRANBERRY (proposed use = 0.50 lb ai/A total application rate, 45-day PHI)[3]									
Cranberry	0.5026-0.5601	43-48	10	<0.015	<0.015	<0.015	<0.008	<0.008	0.0
FLAX (proposed use = 0.188 lb ai/A total application rate, PHI not specified)[2]									
At-planting, broadcast to soil									
Flax, seed	0.093-0.094	89-170	10	<0.01	<0.01	<0.01	0.005	0.005	0.0
	0.185-0.188	89-170	10	<0.01	<0.01	<0.01	0.005	0.005	0.0
Over-the-top broadcast									
Flax, seed	0.094-0.096	46-130	10	<0.01	<0.01	<0.01	0.005	0.005	0.0
MILLET (proposed use = 0.188 lb ai/A total application rate, PHI not specified)[2]									
At-planting, soil surface									
Millet, forage	0.092-0.098	31-70	10	<0.01	<0.01	<0.01	0.005	0.005	0.0
Millet, hay		31-70	10	<0.01	0.013	<0.01	0.005	0.006	0.002
Millet, straw		84-132	10	<0.01	<0.01	<0.01	0.005	0.005	0.0
Millet grain		84-132	10	<0.01	<0.01	<0.01	0.005	0.005	0.0
Millet, forage	0.186-0.194	31-70	10	<0.01	0.014	<0.012	0.005	0.006	0.003
Millet, hay		31-70	10	<0.01	0.011	0.011	0.005	0.006	0.003
Millet, straw		84-132	10	<0.01	<0.01	<0.01	0.005	0.005	0.0
Millet grain		84-132	10	<0.01	<0.01	<0.01	0.005	0.005	0.0

Postemergence, over-the-top									
Millet, forage	0.092-0.097	28-31	10	<0.01	<0.01	<0.01	0.005	0.005	0.0
Millet, hay		28-31	10	<0.01	<0.01	<0.01	0.005	0.005	0.0
Millet, straw		61-113	10	<0.01	<0.01	<0.01	0.005	0.005	0.0
Millet grain		61-113	10	<0.01	<0.01	<0.01	0.005	0.005	0.0

[1] HAFT = Highest-Average Field Trial.
[2] For calculation of the median, mean, and standard deviation 0.005 ppm (half the LOQ) was used for residues reported below the LOQ.
[3] For calculation of the median, mean, and standard deviation, 0.008 ppm (half the calculated LOQ) was used for residues reported below the LOQ.

Berry, group 13

Syngenta Crop Protection has submitted field trial data for mesotrione on the representative crops of the berry group, crop group 13. A total of ten berry trials were conducted during the 2004-2005 growing season. Six blueberry trials were conducted in Regions 1 (NY; 1 trial), 2 (NC; 2 trials), 5 (MI; 2 trials), and 12 (WA; 1 trial); three raspberry trials were conducted in Regions 5 (MI; 1 trial) and 12 (OR; 2 trials); and one blackberry trial was conducted in Region 12 (OR).). The number and location of field trials are acceptable.

At each trial location, a single pre-bloom directed spray application of a 4 lb/gal FlC formulation of mesotrione was made at ~0.094 lb ai/A or ~0.187 lb ai/A (0.5x or 1x the maximum proposed seasonal application rate, respectively). Applications were made using ground equipment in spray volumes of 24-62 gal/A, without an adjuvant. Berries were harvested at maturity, 34-88 days after application. Additional samples were collected from one blueberry and one raspberry trial 7 and 4 days prior to and 4 days after mature harvest (PHIs of 32, 35, and 49 days and 67, 70, and 78 days, respectively) to demonstrate residue decline.

Samples of blueberries, raspberries, and blackberries were analyzed for residues of mesotrione *per se* using a modified version of LC/MS/MS method RAM 366/01. This method was previously reviewed and forwarded to FDA for inclusion in PAM Vol. II as a confirmatory enforcement method for plant commodities (Memo, W. Cutchin, 12-JAN-2005; DP#: 283827). The method is adequate for data collection based on acceptable concurrent recovery data. The validated LOQ was 0.01 ppm for mesotrione in/on berries.

The maximum storage interval of berry samples from harvest to analysis was 501 days (16.4 months). No storage stability data are available, and none were submitted to support the storage intervals and conditions of samples from the berry field trials; however, the petitioner stated that the results of a storage stability study demonstrating the stability of mesotrione residues in/on berries stored frozen for 17 months will be submitted to the Agency upon completion.

The results of the berry crop field trials are presented in Table 6. Residues of mesotrione were below the method LOQ (<0.01 ppm) in/on all blueberry, raspberry, and blackberry samples harvested 34-88 days following a prebloom, directed spray treatment with the 4 lb/gal FlC formulation at 0.091-0.098 lb ai/A or 0.185-0.193 lb ai/A.

Because residues of mesotrione were below the LOQ in/on all blueberry and raspberry samples from the residue decline studies, no conclusions can be made concerning residue decline.

Cranberry

Syngenta Crop Protection has submitted field trial data for mesotrione on cranberry. Five trials were conducted in Regions 1 (MA; 1 trial), 2 (NJ; 1 trial), 5 (WI; 2 trials), and 12 (OR; 1 trial) during the 2004 growing season. The number and location of field trials are acceptable. Although one trial each was conducted in Regions 1 and 2 instead of two trials in Region 1, the Region 2 trial was conducted in NJ cranberry bogs located relatively close to the border of Region 1.

At each trial location, two foliar broadcast applications of a 4 lb/gal FlC formulation of mesotrione were made at ~0.3 lb ai/A for the first application and ~0.2 lb ai/A for the second application, for a total application rate of ~0.5 lb ai/A (1x the maximum proposed seasonal application rate). Applications were made at 13- to 15-day RTIs using ground equipment in spray volumes of 20-29 gal/A. A nonionic surfactant was added to the spray mixtures at all trials except the OR trial, where an insecticidal petroleum oil concentrate was inadvertently used instead of a COC as the spray adjuvant. Mature cranberries were harvested 43-48 days after the last application.

Samples of cranberries were analyzed for residues of mesotrione *per se* using a modified version of LC/MS/MS method RAM 366/01. This method was previously reviewed and forwarded to FDA for inclusion in PAM Vol. II as a confirmatory enforcement method for plant commodities (Memo, W. Cutchin, 12-JAN-2005; DP#: 283827). The LLMV was 0.01 ppm. Based on recoveries at the LLMV, the calculated LOQ and LOD were 0.015 ppm and 0.005 ppm, respectively, for cranberry. This method is adequate for data collection based on acceptable method validation and concurrent recovery data. HED notes that, although the petitioner used the LLMV of 0.01 ppm as the quantitation limit for reporting residue results, based on the calculated LOQ, the method does not reliably quantitate residues down to 0.01 ppm.

The maximum storage interval of cranberry samples from harvest to analysis was 238 days (7.8 months). Storage stability data generated concurrently with the field trials indicate that residues of mesotrione are stable in fortified samples of cranberry stored frozen for up to 217 days (7.1 months). The concurrent storage stability data, in conjunction with available storage stability data which demonstrate that mesotrione is stable in other crops (corn matrices, radish root, and soybean seed) stored frozen for up to 40-44 months (Memo, S. Levy, 06-JUN-2001; DP#: 245477), are adequate to support the storage conditions and intervals of samples from the submitted cranberry field trials.

The results of the cranberry crop field trials are presented in Table 6. Residues of mesotrione were reported as <0.01 ppm in/on all cranberry samples harvested 43-48 days following foliar treatments with the 4 lb/gal FlC formulation at total seasonal rates of 0.503-0.560 lb ai/A.

Residue decline data were not submitted and are not required to support the 43- to 48-day PHI reflected in the field trials.

Flax

Syngenta Crop Protection has submitted field trial data for mesotrione on flax. Five flax trials were conducted in Regions 5 (MN and ND; 2 trials) and 7 (MT, ND, and SD; 3 trials) during the 2004 growing season. The number and location of crop field trials are acceptable.

Each field trial site consisted of one untreated plot and three treated plots. Two plots at each site received a single at-planting, broadcast soil application of a 4 lb/gal FlC formulation of mesotrione at ~0.094 lb ai/A or ~0.187 lb ai/A (0.5x or 1x the maximum proposed seasonal application rate, respectively). At the third plot, the 4 lb/gal FlC formulation was applied as a single over-the-top broadcast application to flax at the 10" growth stage at ~0.094 lb ai/A (no foliar use proposed at this time). Applications were made using ground equipment in 10-30 gal/A, without an adjuvant. Mature flax seed was harvested 89-170 days after treatment (DAT) from the plots treated at-planting, and 46-130 DAT from the plot treated postemergence. To demonstrate residue decline, additional samples were collected from each treatment plot at the SD trial site 7 days before and after mature harvest.

Samples of flax seed were analyzed for residues of mesotrione *per se* using a modified version of LC/MS/MS method RAM 366/01. This method was previously reviewed and forwarded to FDA for inclusion in PAM Vol. II as a confirmatory enforcement method for plant commodities (Memo, W. Cutchin, 12-JAN-2005; DP#: 283827). The method is adequate for data collection based on acceptable concurrent recovery data. The validated LOQ was 0.01 ppm for mesotrione in/on flax seed.

The maximum storage interval of flax seed samples from harvest to analysis was 382 days (12.6 months). The petitioner referenced available storage stability data which demonstrate that mesotrione is stable in corn matrices and soybean seed stored frozen for up to 40-42 months (Memo, S. Levy, 06-JUN-2001; DP#: 245477). The available corn and soybean storage stability data will support the storage conditions and intervals of samples from the subject flax field trials. The results of the flax crop field trials are presented in Table 6. Residues of mesotrione were below the method LOQ (<0.01 ppm) in/on all flax seed samples harvested 89-170 days following a single at-planting, soil-surface broadcast application of a 4 lb/gal FlC formulation at 0.093-0.094 lb ai/A or 0.185-0.188 lb ai/A. Residues of mesotrione were also below the method LOQ (<0.01 ppm) in/on all flax seed samples harvested 46-130 days following a single over-the-top broadcast application of the 4 lb/gal FlC formulation at 0.094-0.096 lb ai/A.

Because residues of mesotrione were below the LOQ in/on all flax seed samples from the residue decline study, no conclusions can be made concerning residue decline.

Millet

Syngenta Crop Protection has submitted field trial data for mesotrione on millet. Five millet trials were conducted in Regions 5 (IL; 1 trial), 7 (NE and SD; 2 trials) and 8 (CO; 2 trials) during the 2004 growing season. The number and location of field trials are acceptable.

Each field site consisted of one untreated plot and three treated plots. Two plots at each site received a single at-planting, broadcast soil application of a 4 lb/gal FlC formulation of mesotrione at ~0.094 lb ai/A or ~0.187 lb ai/A (0.5x or 1x the maximum proposed seasonal

application rate). At the third plot, the 4 lb/gal FlC formulation was applied as a single over-the-top broadcast application to millet at the 6" growth stage at ~0.094 lb ai/A (no foliar use proposed at this time). Applications were made using ground equipment in 13-20 gal/A. Spray adjuvants were used for the over-the-top applications at the NE site (nonionic surfactant) and SD site (COC) only. Immature forage and hay were harvested 31-70 DAT from plots treated at-planting, and 28-31 DAT from the plots treated postemergence. Mature straw and grain were harvested 84-132 DAT from the plots treated at-planting and 61-113 DAT from the plot treated postemergence. To demonstrate residue decline additional samples were collected from a single trial at ~7 days before and after the target harvest interval from all treatment regimes.

Samples of millet forage, hay, straw, and grain were analyzed for residues of mesotrione *per se* using a modified version of LC/MS/MS method RAM 366/01. This method was previously reviewed and forwarded to FDA for inclusion in PAM Vol. II as a confirmatory enforcement method for plant commodities (Memo, W. Cutchin, 12-JAN-2005; DP#: 283827). The method is adequate for data collection based on acceptable concurrent recovery data. The validated LOQ for this method was 0.01 ppm for mesotrione in/on millet matrices.

The maximum storage interval of millet samples from harvest to analysis was 415 days (13.7 months). The petitioner referenced available storage stability data which demonstrate that mesotrione is stable in corn matrices and soybean seed stored frozen for up to 40-42 months (Memo, S. Levy, 06-JUN-2001; DP#: 245477). The available corn and soybean storage stability data will support the storage conditions and intervals of samples from the subject millet field trials.

The results of the millet crop field trials are presented in Table 6. Residues of mesotrione were below the method LOQ (<0.01 ppm) following a single at-planting, broadcast soil application of the 4 lb/gal FlC formulation at 0.092-0.098 lb ai/A in/on all samples of millet forage, hay, straw, and grain, except one sample of hay, which bore residues of 0.013 ppm. Maximum residues of mesotrione were 0.014 ppm in/on millet forage and 0.011 ppm in/on hay samples following a single at-planting, broadcast soil application at 0.186-0.194 lb ai/A; residues were below the method LOQ (<0.01 ppm) in/on all millet straw and grain samples following this treatment.

Residues of mesotrione were below the method LOQ (<0.01 ppm) in/on all millet forage, hay, straw, and grain samples following a single over-the-top broadcast application of the 4 lb/gal FlC formulation at 0.092-0.097 lb ai/A.

In the residue decline study, residues of mesotrione were below the LOQ following application at-planting (both rates) in/on all millet forage, hay, straw and grain samples. Following postemergence application, residues of mesotrione were below the LOQ in/on all millet straw and grain samples. Low quantifiable residues were observed at the 23-day PHI in millet forage (0.010 ppm) and hay (0.013 ppm), but residues declined to below the LOQ by the 30-day target PHI.

Grain Sorghum

There are no existing grain sorghum tolerances. The KS Department of Agriculture has proposed that the residue data supporting the existing tolerances for mesotrione on corn be used to set the time-limited tolerances on grain sorghum. The LOQ for mesotrione on corn is 0.01 ppm. The maximum proposed use rate for mesotrione on grain sorghum under this proposed Section 18 is only 33% of the use rate used to set the tolerances in corn. Additionally, the corn tolerance is based, in part, on post-emergence applications at the 8-leaf stage, while the grain sorghum use pattern is 7- to 14-days pre-plant with no post-plant applications allowed. Specifically, the proposed grain sorghum use rate is 0.168 lb ai/A applied 7- to 14-days pre-plant. The existing mesotrione tolerance on corn is based on a pre-plant application of 0.30 lb ai/A and a second application at 0.20 lb ai/A post-emergence for a total application rate of 0.50 lb ai/A. Corn and sorghum are similar in their growth pattern, biomass, planting and harvest times, and are expected to be similar in their metabolic profile. For purposes of this Section 18 registration only, the corn residue data will be translated to grain sorghum.

Conclusions. The cranberry, flax, and millet studies are acceptable. The berry study is tentatively classified as acceptable pending submission of the results of an acceptable storage stability study for residues of mesotrione in/on berries.

The submitted data will support tolerances for residues of mesotrione in/on flax seed and millet grain and straw at 0.01 ppm, and in/on millet forage and hay at 0.02 ppm. Based on the calculated LOQ, the submitted data will support a tolerance of 0.02 ppm for cranberry. Pending submission of the outstanding storage stability data, the submitted field trial data will support a tolerance for berry, group 13 at 0.01 ppm.

The established tolerances for residues of mesotrione *per se* in/on corn commodities are appropriate for translation for this Section 18 request on grain sorghum; therefore, HED recommends the following time-limited tolerances: sorghum, grain at 0.01 ppm; sorghum, forage at 0.50 ppm; and sorghum, stover at 1.5 ppm.

860.1520 Processed Food and Feed

DER Reference: 46726303.de2.doc

Flax

Syngenta Crop Protection has submitted a processing study with mesotrione on flax. In one trial conducted in ND during the 2004 growing season, flax seed was harvested 103 days following a single postemergence, over-the-top broadcast application of the 4 lb/gal FlC formulation at 0.094, 0.283, or 0.473 lb ai/A (1x, 3x, or 5x the maximum proposed application rate). Samples of mature flax seed from the 1x and 5x treatments were processed into meal using simulated commercial procedures.

Samples of flax seed and meal were analyzed for residues of mesotrione *per se* using a modified version of LC/MS/MS method RAM 366/01. This method was previously reviewed and forwarded to FDA for inclusion in PAM Vol. II as a confirmatory enforcement method for plant commodities (Memo, W. Cutchin, 12-JAN-2005; DP#: 283827). The method is adequate for

data collection based on concurrent recovery data. The validated LOQ was 0.01 ppm for mesotrione in/on flax seed and meal.

The maximum storage intervals of crop samples, from harvest/processing to analysis, were 330 days (10.9 months) for flax seed and 271 days (8.9 months) for processed meal. The petitioner referenced available storage stability data which demonstrate that mesotrione is stable in corn matrices and soybean seed stored frozen for up to 40-42 months (Memo, S. Levy, 06-JUN-2001; DP#: 245477). The available corn and soybean storage stability data will support the storage conditions and intervals of RAC samples from the flax seed processing study. Because residues were nonquantifiable in the RAC following treatment at 5x the field trial rate, and a processing study would not typically have been required, HED will not require supporting storage stability data for the processed meal samples.

The results of the flax seed processing study are summarized in Table 7. Residues of mesotrione were below the method LOQ (<0.01 ppm) in/on flax seed (RAC) harvested 103 days after a single over-the-top broadcast application with the 4 lb/gal FlC formulation at 0.094 lb ai/A or 0.473 lb ai/A. Residues of mesotrione were also below the method LOQ (<0.01 ppm) in meal processed from flax seed treated at 1x and 5x the field trial application rate. Processing factors for mesotrione could not be calculated because residues were below the LOQ in/on the RAC and the processed commodity.

Table 7. Summary of Processing Factors for Mesotrione.

RAC	Processed Commodity	Total Rate (lb ai/A)	Processing Factor
Flax seed	Flax meal	0.094 (1x)	NC
		0.473 (5x)	NC

Grain Sorghum

There are no processed commodities for grain sorghum that require tolerances at this time.

Conclusions. The submitted flax processing study is acceptable. Because residues were below the LOQ in/on all samples of flax seed and meal following application of mesotrione to flax at 1x and 5x the maximum proposed seasonal application rates, a tolerance for residues in flax meal is not required. The proposed tolerance of 0.01 ppm for flax seed will cover any anticipated residues in flax meal.

860.1650 Submittal of Analytical Reference Standards

An analytical standard for mesotrione is currently available in the National Pesticide Standards Repository (personal communication with Dallas Wright, ACL/BEAD, 20-SEP-2006). Analytical reference standard of mesotrione should be replenished as requested by the Repository. The reference standards should be sent to the Analytical Chemistry Lab, which is located at Fort Meade, to the attention of either Theresa Cole or Frederic Siegelman at the following address:

USEPA
National Pesticide Standards Repository/Analytical Chemistry Branch/OPP
701 Mapes Road
Fort George G. Meade, MD 20755-5350

(Note that the mail will be returned if the extended zip code is not used.)

860.1850 Confined Accumulation in Rotational Crops

DER Reference: None
Memo, S. Levy, 26-APR-2001; DP#: 274111
Memo, S. Levy, 06-JUN-2001; DP#: 245477

No new confined rotational crop studies were submitted with this petition. An adequate confined rotational crop study was submitted under the previous petition (Memo, S. Levy, 06-JUN-2001; DP#: 245477) for field corn uses. TRR expressed as [^{14}C]mesotrione equivalents, accumulated at levels ≥0.01 ppm in the following rotational crop commodities of soybeans and wheat planted in sandy loam soil 30 DAT with uniformly ring-labeled phenyl (PH) or cyclohexane-labeled (CY) [^{14}C]mesotrione at 0.274 lb ai/A (1.1x the maximum proposed/registered pre-emergence application rate for corn): soybean forage, hay, and soybeans, and wheat forage, hay, straw, and grain. TRR in PH samples ranged from 0.038 ppm in wheat grain to 2.58 ppm in wheat straw; in CY samples TRR were lower, ranging from 0.010 ppm in wheat grain to 0.059 ppm in wheat straw.

Based on the components identified, the results of the confined rotational crop study suggest that mesotrione is metabolized in rotational crops via a route similar to that demonstrated in primary crops. HED previously concluded that for tolerance expression and risk assessment purposes, the residue of concern in/on rotational crop commodities is mesotrione *per se* (Memo, S. Levy, 26-APR-2001; DP#: 2741411).

860.1900 Field Accumulation in Rotational Crops

DER Reference: None
Memo, S. Levy, 06-JUN-2001; DP#: 245477

No new field rotational crop data were submitted with this petition. An acceptable limited field rotational crop study was submitted under the previous petition for field corn uses. Residues of mesotrione and its metabolite MNBA were each less than the method LOQ (<0.01 ppm) in/on all rotational crop matrices (radish roots and tops; soybean forage, hay, and seed; millet forage, hay, straw, and grain; and sorghum forage) from the 29- to 30-day PBI following a single preplant incorporated application made to the primary crop, field corn, of the 4 lb/gal FlC formulation at 0.30 lb ai/A/application (~0.9x maximum proposed seasonal rate to sweet corn). Residues of mesotrione and its metabolite MNBA were each less than the method LOQ (<0.01 ppm) in/on all rotational crop matrices (radish roots and tops; endive leaves; and wheat forage, hay, straw, and grain) from the 74- to 100-day PBI following two applications (preplant incorporated and postemergence) made to the primary crop, field corn, of the 4 lb/gal FlC formulation at a total rate of 0.50 lb ai/A (~1.5x maximum proposed seasonal rate).

The available field rotational crop data support the proposed PBIs listed on the product label for Callisto® Herbicide: (i) 120 days for small grains; (ii) 10 months for soybeans, sorghum, cotton, peanuts, potatoes, sunflowers, canola, tobacco, and alfalfa; and (iii) 18 months for sugar beets, peas, dry beans, snap beans, cucurbits, red clover, and all other rotational crops.

860.1550 Proposed Tolerances

Current tolerances for field, pop, and sweet corn commodities are expressed in terms of residues of the herbicide mesotrione *per se*, 2-[4-(methylsulfonyl)-2-nitrobenzoyl]-1,3-cyclohexanedione [40 CFR §180.571].

In support of the proposed uses, the petitioner has proposed to establish tolerances for residues of mesotrione *per se* on berry group, cranberry, flax seed, flax meal, and millet grain, forage, hay, and straw. The proposed, and HED-recommended, tolerances are presented in Table 8.

Adequate field trial data are available for cranberries, flax, and millet; additional storage stability data are required to support the berry field trials. Provided the petitioner amends the proposed label by removing recommendations for use of a spray adjuvant for applications to flax and millet, or provides evidence that a surfactant was used in the spray mixtures in the submitted crop field trials, the available field trial data will support tolerances for residues of mesotrione *per se* in/on flax seed, and millet grain and forage at 0.01 ppm and in/on cranberry and millet straw and hay at 0.02 ppm. Pending submission of the outstanding storage stability data, and provided the petitioner amends the proposed label by removing recommendations for use of a spray adjuvant for applications to berry, group 13, or provides evidence that a surfactant was used in the spray mixtures in the submitted crop field trials, the berry field trial data will support a tolerance for berry, group 13 at 0.01 ppm. HED notes that, pending revisions to the berry crop group, a separate tolerance should be established for lingonberry (Memo, B. Schneider, 14-JUN-2002; No DP#).

The established tolerances for residues of mesotrione *per se* in/on corn commodities are appropriate for translation for this Section 18 request on grain sorghum; therefore, HED recommends the following time-limited tolerances for residues of mesotrione *per se* in/on: sorghum, grain, grain at 0.01 ppm; sorghum, grain, forage at 0.50 ppm; and sorghum, grain, stover at 1.5 ppm.

Adequate processing data for flax meal are available. The data indicate that residues of mesotrione are not likely to concentrate in flax meal; therefore, the proposed tolerance for flax meal is not needed.

The Tolerance/Maximum Residue Limit (MRL) Harmonization Spreadsheet was not used to derive tolerances for this action because residues in the majority of matrices tested were below the LOQ.

No Codex or Mexican MRLs have been established for mesotrione, and no Canadian MRLs have been established for the subject crops; the residue definition for Canadian MRLs is also parent only.

The proposed tolerances should be revised to reflect the HED-recommended tolerance levels and correct commodity definitions as specified in Table 8. **A revised Section F should be submitted.**

Table 8. Tolerance Summary for Mesotrione.

Commodity	Established/Proposed Tolerance (ppm)	Recommended Tolerance (ppm)	Comments; *Correct Commodity Definition*
Flax, seed	0.01	0.01	
Flax, meal	0.01	None required	The proposed tolerance for flax seed will cover residues in flax meal
Millet, grain	0.01	0.01	
Millet, forage	0.01	0.01	
Millet, hay	0.02	0.02	
Millet, straw	0.02	0.02	
Berry group	0.01	0.01	*Berry, group 13*
	NA	0.01	*Lingonberry*
Cranberry	0.01	0.02	
Sorghum, grain	NA	0.01	*Sorghum, grain, grain*
Sorghum, forage	NA	0.50	*Sorghum, grain, forage*
Sorghum, stover	NA	1.5	*Sorghum, grain, stover*

References

DP#: 260570
Subject: PP#8F04954. Mesotrione (Proposed Name). Multiresidue Method Testing of ZA1296. Chemical #: 122990. Case #: 289589. Submission #: S541377
From: S. Levy
To: F. Griffith
Date: 16-NOV-1999
MRID#: 44505224

DP#: 263245
Subject: Product Chemistry Review of Mesotrione (ZA 1296 Technical (dry)).
From: H. Podall
To: J. Tompkins/J. Stone
Date: 24-FEB-2000
MRID#s: 44373503-44373505, 44505003, 44505004, and 44901701

DP#: 274111
Subject: PP# 8F04954. Mesotrione: Health Effects Division (HED) Metabolism Assessment Review Committee (MARC) Meeting of 4/10/01. Chemical No. 122990. Case No. 063670. Submission No. S541375.
From: S. Levy
To: Y. Donovan
Date: 26-APR-2001
MRID#: None

DP#s: 245477 and 260267
Subject: PP#: 8F04954. Mesotrione in/on Field Corn. Evaluation of Residue Data and Analytical Methods. PC Code: 122990. Case #: 289589. Submission #s: S541377 and S569871.
From: S. Levy
To: J. Stone /J. Tompkins
Date: 06-JUN-2001
MRID#s: 44505118, 44505212-23, 44537109-12, 44901719, and 44942401-03

DP#: None
Subject: Reviewer's Guide and Summary of HED ChemSAC Approvals for Amending Commodity Definitions [40 CFR §180.1(h)] and Crop Group/Subgroups [40 CFR §180.41].
From: B. Schneider
To: H. Jamerson
Date: 14-JUN-2002
MRID#: None

DP#: 283827
Subject: Mesotrione. Summary of Analytical Chemistry and Residue Data for Sweet Corn, PP#2F06443, and Response to Data Deficiencies of a Previous HED Review (PP#8F04954, DP Barcodes: D245477 and D260267, 6/6/01, S. Levy).
From: W. Cutchin
To: J. Stone/J. Miller
Date: 12-JAN-2005
MRID#s: 45651801-45651803, 45651813, 45651814, 45651816, 45651817, and 45665901

Attachments

Attachment 1: International Residue Limit Status (IRLS) sheet
Attachment 2: Chemical Structures

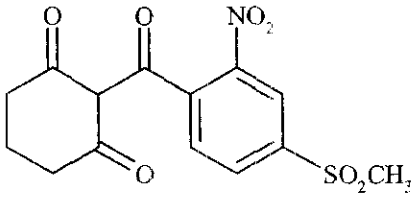
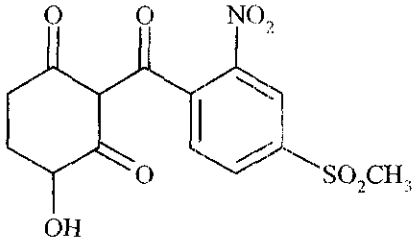
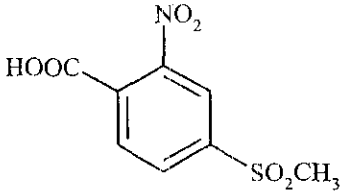
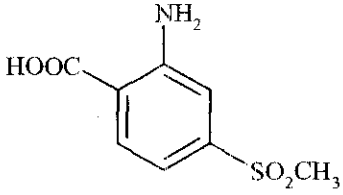
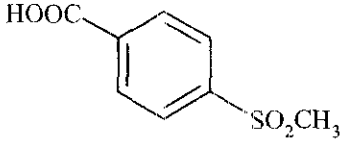
cc: S.Levy
RDI: G.F. Kramer (02-MAR-2007), RAB1 Chemists (06-DEC-2006),
S. Levy:S-10953:PY1:(703)305-0783:7509P:RAB1
Petition#s: 6F7023, 06KS01
DP#s: 326898, 332812
PC Code: 122990

Template Version September 2005

Attachment 1: IRLS sheet

INTERNATIONAL RESIDUE LIMIT STATUS			
Chemical Name: 2-[4-(methylsulfonyl)-2-nitrobenzoyl]-1,3-cyclohexanedione	Common Name: Mesotrione	X Proposed tolerance 9 Reevaluated tolerance 9 Other	Date: 20-SEP-2006
Codex Status (Maximum Residue Limits)		U. S. Tolerances	
X No Codex proposal step 6 or above 9 No Codex proposal step 6 or above for the crops requested		Petition#: 6F7023 DP#: 326898 Other Identifier:	
Residue definition (step 8/CXL): N/A		Reviewer/Branch: RAB1; Sarah Levy	
		Residue definition: mesotrione (2-[4-(methylsulfonyl)-2-nitrobenzoyl]-1,3-cyclohexanedione; designated by the company code ZA1296)	
Crop (s)	MRL (mg/kg)	Crop(s)	Tolerance (ppm)
		Flax, seed	0.01
		Flax, meal	0.01
		Millet, grain	0.01
		Millet, forage	0.01
		Millet, hay	0.02
		Millet, straw	0.02
		Berry group	0.01
		Cranberry	0.01
Limits for Canada		Limits for Mexico	
X No Limits for the crops requested		X No Limits	
Residue definition: 2-[4-(methylsulfonyl)-2-nitrobenzoyl]-1,3-cyclohexanedione		Residue definition: N/A	
Crop(s)	MRL (mg/kg)	Crop(s)	MRL (mg/kg)
Notes/Special Instructions: S .Funk, 21-SEP-2006.			

Attachment 2: Chemical Structures

APPENDIX I. Chemical Names and Structures		
Common name; Company code	Chemical name	Chemical structure
Mesotrione; ZA 1296	2-[4-(methylsulfonyl)-2-nitrobenzoyl]-1,3-cyclohexanedione	
4-OH-mesotrione; R282813	4-hydroxy-2-[4-(methylsulfonyl)-2-nitrobenzoyl]-1,3-cyclohexanedione	
MNBA	4-methanesulfonyl-2-nitro-benzoic acid	
AMBA	2-amino-4-methanesulfonyl-benzoic acid	
MBA	4-methanesulfonyl-benzoic acid	

Primary Evaluator: Sarah J. Levy, Chemist
Registration Action Branch (RAB1)
Health Effects Division (HED) (7509P)

Date: 02-MAR-2007

Approved by: George F. Kramer, Ph.D., Senior Chemist
RAB1/HED (7509P)

Date: 02-MAR-2007

This data-evaluation record (DER) was originally prepared under contract by Dynamac Corporation (2275 Research Boulevard, Suite 300; Rockville, MD 20850; submitted 29-SEP-2006). The DER has been reviewed by the HED and revised to reflect current Office of Pesticide Programs (OPP) policies.

STUDY REPORTS:

46726304 Rumback, D. (2003) [Cylohexane-2-^{14}C]: Nature of the Residue in Peanuts: Final Report. Project Number: 1287-01. Unpublished study prepared by Syngenta Crop Protection, Inc. 113 p.

46726305 Brown, K. (2003) [Phenyl-U-^{14}C] Mesotrione: Nature of the Residue in Peanuts: Final Report. Project Number: 1286-01. Unpublished study prepared by Syngenta Crop Protection, Inc., Syngenta Crop Protection and Syngenta Crop Protection. 169 p.

EXECUTIVE SUMMARY:

Syngenta Crop Protection, Inc. has submitted two studies investigating the metabolism of [cyclohexane-2-^{14}C]mesotrione (CY label; specific activity 40.1 µCi/mg) and [phenyl-U-^{14}C]mesotrione (PH label; specific activity 40.5 µCi/mg) in peanuts. In separate studies, the radiolabeled test substances were formulated and applied as a single preemergence application one day after planting peanut seed at nominal rates of 0.29 lb ai/A (327 g ai/ha) and 0.75 lb ai/A (836 g ai/ha) for the CY label, and 0.27 lb ai/A (305 g ai/ha) and 0.71 lb ai/A (796 g ai/ha) for the PH label. The petitioner reported minor phytotoxic effects in peanuts treated at the high rate for both labels. Samples of peanut foliage were collected at 50% mature harvest, 90 days after application, and samples of mature peanut hay and peanuts were collected 154 days after application. Peanuts were separated into hulls and nutmeat following harvest.

Total radioactive residues (TRR) in peanut matrices were determined by combustion/liquid-scintillation counting (LSC). Following application of CY-labeled mesotrione at 0.29 lb ai/A, TRR were 0.006 ppm in 50% mature foliage, 0.004 ppm in hay, and 0.005 and 0.007 ppm in hulls and nutmeat, respectively. Following application at 0.75 lb ai/A, TRR were 0.020 ppm in foliage, 0.011 ppm in hay, and 0.015 and 0.022 ppm in hulls and nutmeat, respectively. Following application of PH-labeled mesotrione at 0.27 lb ai/A, TRR were 0.028 ppm in 50% mature foliage, 0.012 ppm in hay, and 0.011 and 0.013 ppm in hulls and nutmeat, respectively. Following application at 0.71 lb ai/A, TRR were 0.064 ppm in foliage, 0.028 ppm in hay, and 0.025 and 0.037 ppm in hulls and nutmeat, respectively. In the CY-label study, only samples

from the high rate were subjected to further extraction and analysis for characterization of residues.

In the CY-label study, solvent extraction with acetonitrile (ACN)/water released ~43%, 27%, and 20% TRR in 50% mature foliage, hay, and hulls respectively. No further attempts were made to release radioactivity from these matrices; nonextractable residues were 65.9-84.5% TRR (0.008-0.013 ppm). Nutmeats were subjected to two separate extraction procedures intended to resolve polar and nonpolar residues. In the first procedure, extraction with ACN/water and ethyl acetate released 43.5% TRR (0.012 ppm); in the second procedure, extraction with hexane and ethyl acetate released 51.4% TRR (0.011 ppm). Nonextractable residues in nutmeat, accounting for 50.8% TRR (~0.011 ppm), were not further investigated. Although nonextractable residues accounting for ≥50% TRR in all matrices were not further investigated, HED concludes that the extraction procedures were adequate because TRR were low in all peanut matrices, and metabolism of mesotrione appeared to be extensive. Residues were identified and quantitated by high-performance liquid chromatography (HPLC) following further characterization via anion-exchange chromatography or solid-phase extraction (SPE) on an amino column (for nutmeats).

In the PH-label study, solvent extraction with ACN/water released ~41-42%, 32-34%, and 20-23% TRR in low- and high-rate 50% mature foliage, hay, and hulls respectively. Additional radioactivity was released from the nonextractable residues by refluxing with water followed by acid and base hydrolysis. These procedures released ~27-52%, 41-42%, and 31-38% TRR in low- and high-rate foliage, hay, and hulls. Remaining nonextractable residues, accounting for 13%, 26%, and 46% TRR (0.003-0.005 ppm) in low-rate foliage, hay, and hulls and for 26%, 24%, and 20% TRR (0.005-0.016 ppm) in high-rate foliage, hay, and hulls, were characterized as cellulose or lignins on the basis of base and acid hydrolysis. For nutmeats, extraction with hexane released 36% and 32% TRR (0.005 and 0.012 ppm) in low- and high-rate samples, respectively. Additional radioactivity was released from the nonextractable residues by refluxing with water followed by acid and base hydrolysis. These procedures released ~92% TRR in low-rate nutmeats and ~29% TRR in high-rate nutmeats; remaining nonextractable residues, accounting for 16% TRR in low-rate nutmeats and 50% TRR (0.018 ppm) in high-rate nutmeats, were characterized as cellulose or lignin. The extraction procedures for the PH-label study were adequate. Residues were identified and quantitated by HPLC and identification of metabolites was confirmed by thin-layer chromatography (TLC) co-chromatography.

Accountabilities, based on extraction procedures ranged 100-107% for the CY-label study. In the PH-label study, accountabilities ranged 92-114% for low- and high-rate foliage and hay, low-rate hulls, and high-rate nutmeats; accountabilities of 76% and 146% were obtained for high-rate hulls and low-rate nutmeats, respectively. The petitioner made no attempt to explain the low recovery observed for high-rate hulls or the excessively high recovery obtained for low-rate nutmeats, which resulted from high reported TRR in the aqueous and organic phases following dichloromethane (DCM) partitioning of the acidified hydrolysate of the nonextractable residues. HED furthermore notes, that the petitioner did not address the loss of radioactivity on further characterization/identification analysis following extraction procedures and did not provide quantitative data for minor unknowns for any fraction except the aqueous fraction following initial partitioning of the ACN/water phase.

Adequate storage stability data were submitted to support the storage intervals and conditions of raw agricultural commodities (RAC) samples and extracts from the CY- and PH-label studies.

Mesotrione was not identified in any peanut matrix following preemergence application of CY-labeled mesotrione at 0.75 lb ai/A. The only identified metabolite was 4-OH-mesotrione, at 1.6% and 1.4% TRR in 50% mature foliage and hay, respectively, and 0.5% TRR in hulls. Identification of this metabolite was adequately confirmed by liquid chromatography (LC)/mass spectrometry (MS) and a number of additional procedures. Minor unknowns (none present at ≥0.001 ppm in any matrix) accounted for 15.1%, 6.0%, and 3.3% TRR in foliage, hay, and hulls, and remaining radioactivity was characterized on the basis of anion-exchange chromatography (such as neutral/basic, neutral/acidic, or acidic) and distribution into organic solvents (including ACN, methanol, and ethanol) or aqueous phases. In peanut nutmeats, the distribution of polar residues was similar to that in the other matrices. Nonpolar residues in nutmeats were characterized as neutral lipids (37.8% TRR, 0.008 ppm), fatty acids (5.7% TRR, 0.001 ppm), and phospholipids (4.1% TRR, 0.001 ppm) on the basis of elution characteristics on amino SPE. The petitioner confirmed the presence of fatty acids via additional characterization procedures using radiolabeled standards of glycerol and triacylglycerides labeled in the fatty acid portion of the molecule.

The metabolite profile following preemergence application of PH-labeled mesotrione differed from the profile observed in the CY-label study. Although mesotrione was not identified in any matrix from either treatment rate, metabolites MNBA (4-methanesulfonyl-2-nitro-benzoic acid) and AMBA (2-amino-4-methanesulfonyl-benzoic acid) were identified in all matrices, MBA was identified in foliage, hay, and nutmeat, and 4-OH-mesotrione was identified in nutmeat only. MNBA accounted for 12.4% TRR (0.003 ppm), 5.1% TRR (0.001 ppm), and 3.6% TRR (<0.001 ppm) in low-rate foliage, hay, and hulls, respectively, and was not identified in low-rate nutmeat. In high-rate matrices, MNBA accounted for 11.1% TRR (0.007 ppm), 6.4% TRR (0.002 ppm), 9.6% TRR (0.002 ppm), and 2.4% TRR (0.001 ppm) in high-rate foliage, hay, hulls, and nutmeat, respectively. AMBA was identified in all matrices treated at low- and high-rates, respectively, at 16.7% and 7.1% TRR (0.005 ppm each) in foliage, 6.9% and 4.6% TRR (0.001 ppm each) in hay, 1.6% and 1.4% TRR (<0.001 ppm each) in hulls, and 15.0% and 1.4% TRR (0.002 and 0.001 ppm) in nutmeats. MBA was identified at 0.6% TRR (<0.001 ppm) in high-rate foliage, 3.2% and 2.8% TRR (<0.001 ppm each), respectively, in low- and high-rate hay, and at 6.7% TRR (0.001 ppm) in low-rate nutmeat. 4-OH-Mesotrione was identified in low-rate nutmeat at 6.9% TRR (0.001 ppm). Additional residues were characterized as cellulose and lignins on the basis of hydrolysis in all matrices as noted above, and, as in the CY-label studies, residues in low- and high-rate nutmeats were characterized as neutral lipids, fatty acids, and phospholipids on the basis of elution characteristics on amino SPE; the neutral lipid residues were further characterized on a second amino SPE column. Based on these analyses, residues in low- and high-rate nutmeats, respectively, were characterized as cholesterol esters (12.8% and 2.7% TRR), triacylglycerols (17.4% and 23.5% TRR), and monoacylglycerols (7.0% and 7.3% TRR), fatty acids (4.7% and 6.5% TRR), and phospholipids (7.0% TRR and trace). One major polar unknown, Peak 1, was found in all matrices from low- and high-rate treatments, respectively, at 17.6% and 11.2% TRR in foliage, 13.1% and 32.1% TRR in hay, 8.6% and

12.4% TRR in hulls, and 14.0% and 7.0% TRR in nutmeat. Peak 1 is believed to consist of AMBA conjugates. Discrete unknowns (identified on the basis of fraction collection by vial numbers) accounted for 1.9-11.4% TRR (≤0.003 ppm) in low- and high-rate foliage, hay, and hulls, and low-rate nutmeat, and minor unknowns (none present at ≥0.001 ppm in any matrix) accounted for at least 1.0-1.6% TRR in foliage, hay, and hulls from both rates. Remaining radioactivity was characterized on the basis of distribution into organic solvents (including ACN, methanol, and ethanol) or aqueous phases.

Based on the submitted CY-label metabolism study, the petitioner proposed that mesotrione is metabolized in peanuts by two pathways. In the first pathway, the cyclohexanedione ring is degraded to CO_2 which is incorporated into natural products, and in the second pathway, the cyclohexanedione ring is oxidized to form 4-hydroxy-mesotrione which is further metabolized to form multiple metabolites. For PH-labeled mesotrione, metabolism proceeds via cleavage of the cyclohexanedione ring to yield MNBA. MNBA is reduced to its amino analog, AMBA, which is subsequently converted to numerous conjugates or further degraded to MBA. As was observed for the CY label, mesotrione may also undergo hydroxylation to form 4-OH-mesotrione. With the exception of 4-OH-mesotrione, metabolites containing both ring moieties were not characterized in either metabolism study. HED notes that these results are similar to those observed in field corn following treatment with CY- and PH-labeled mesotrione (Memo, S. Levy, 06-JUN-2001; DP#: 245477).

STUDY/WAIVER ACCEPTABILITY/DEFICIENCIES/CLARIFICATIONS:

Under the conditions and parameters used in the study, the corn plant metabolism data are classified as scientifically acceptable. The acceptability of this study for regulatory purposes is addressed in the forthcoming U.S. EPA Residue Chemistry Summary Document [DP#: 326898].

COMPLIANCE:

Signed and dated Good Laboratory Practice (GLP), Quality Assurance and Data Confidentiality statements were provided. No deviations from regulatory requirements were reported which would have an impact on the validity of the study.

A. BACKGROUND INFORMATION

Mesotrione is a triketone herbicide which inhibits the enzyme *p*-hydroxyphenylpyruvate dioxygenase (HPPD), disrupting carotenoid biosynthesis. This process leads to the destruction of chlorophyll, resulting in a bleaching effect in susceptible plants. Mesotrione is intended for preemergence and postemergence use for selective control of annual broadleaf weeds. Mesotrione is currently registered for use on field, pop, and sweet corn.

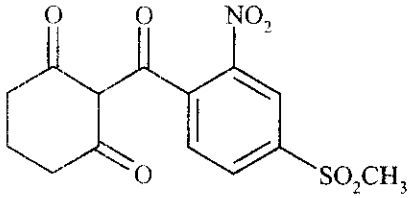
TABLE A.1. Mesotrione Nomenclature.	
Chemical structure	
Common name	Mesotrione
Company experimental name	ZA1296
IUPAC name	2-(4-mesyl-2-nitrobenzoyl)cyclohexane-1,3-dione
CAS name	2-[4-(methylsulfonyl)-2-nitrobenzoyl]-1,3-cyclohexanedione
CAS registry number	104206-82-8
End-use product (EP)	4 lb/gal flowable concentrate (FlC; Callisto® Herbicide; EPA Reg. No. 100-1131)

TABLE A.2. Physicochemical Properties of Mesotrione.		
Parameter	Value	Reference
Melting range	148.7-152.5°C	Memo, H. Podall, 24-FEB-2000; DP#: 263245
pH	3.4 (1% dispersion in water; 25°C)	
Density	1.46 g/mL, 20°C	
Water solubility	20°C 160 ppm, unbuffered water 0.22 g/100 mL, pH 4.8 1.5 g/100mL, pH 6.9 2.2 g/100 mL, pH 9	
Solvent solubility	20°C 0.37 g/100 mL, methanol 1.7 g/100 mL, ethyl acetate 0.27 g/100 mL, toluene 10.4 g/100 mL, acetonitrile <0.03 g/100 mL, heptane 8.1 g/100 mL, acetone	
Vapor pressure	4.3 x 10^{-8} torr, 20°C	
Dissociation constant, pK_a	3.12, 20°C	
Octanol/water partition coefficient, Log(K_{OW})	20°C log P_{OW} = 0.11 in unbuffered water log P_{OW} = 0.90 in pH 5 buffer log P_{OW} <-1 at pH 7 and 9 buffered water	
UV/visible absorption spectrum	Absorption maximum in methanol at 256 mu, with a molar extinction coefficient of 2.24 x 104 M cm.	

B. EXPERIMENTAL DESIGN

B.1. Trial Site and Crop Information

The field site was located at the Syngenta Southern Regional Technical Center (Leland, MS). A summary of the trial site information is provided in Table B.1.1, and a summary of the crop information is provided in Table B.1.2. Peanut seed was planted in outdoor test plots, and the plants were cultivated by hand.

The petitioner provided information concerning plot history and cultivation procedures, and stated that crops were maintained according to normal agricultural practices, including use of pest control and irrigation as needed. Daily rainfall was reported for the duration of the in-life phase, and 5-year weather data (temperature, relative humidity, and precipitation) were provided. The petitioner noted that rainfall during the study period was 10" higher than the previous 5-year average, but did not observe any negative effect on the study. Sprinkler irrigation was applied once during the study.

Peanuts treated at the exaggerated rate were stunted compared to the control plants and those that had been treated at the low-rate. The plants eventually recovered and reached maturity later than the other plants. Also, 5 days after application, plants in certain sub-plots from both studies intercepted herbicide drift (glyphosate trimesium, paraquat, and metolachlor) from maintenance sprays in adjacent areas. According to the petitioner, crop injury from the drift was minimal and did not affect the study. The petitioner concluded that no events occurred during the in-life phase that would be expected to affect the integrity or outcome of the study.

TABLE B.1.1. Trial Site Information.

Type	Method	Soil characteristics[1]			
		Type	%OM	pH	CEC
Soil treatment	A single preemergence application with each test substance at each rate was made to soil in outdoor plots 1 day after planting peanut seed.	Silt loam	0.7	7.0	6.6 meq/100 g

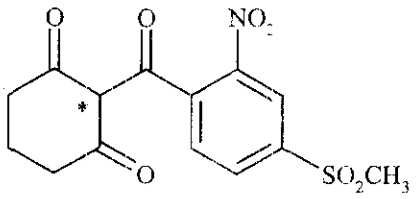
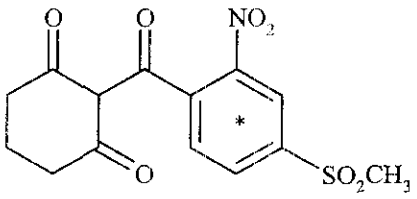
[1] OM = organic matter; CEC = cation-exchange capacity.

TABLE B.1.2. Crop Information.

Crop; crop group	Variety	Growth stage at application	Growth stage at harvest	Harvested Matrix
Peanut (no crop group)	Sepeco NCV-11	N/A: preemergence application (1 day after planting)	50% maturity	Foliage
			Mature	Hay and peanuts

B.2. Test Materials

The radiolabeled test substances were solubilized in ACN, then formulated as flowable concentrate formulations by diluting with formulation blank in water. The test material characteristics are presented in Table B.2.1.

TABLE B.2.1. Test Material Characteristics.		
Chemical structure		
Radiolabel position	[cyclohexane-2-^{14}C]mesotrione	[phenyl-U-^{14}C]mesotrione
Lot No.	CL-L-84	CL-L-82
Purity	97.8% radiochemical purity by TLC	98.5% radiochemical purity by TLC
Specific activity	40.1 µCi/mg	40.5 µCi/mg

B.3. Study Use Pattern

The formulated test substances were diluted with water and applied using a custom-made backpack sprayer as a preemergence application to the soil one day after planting peanut seed. The application rates were 0.29 and 0.75 lb ai/A for CY-labeled mesotrione, and 0.27 and 0.71 lb ai/A for PH-labeled mesotrione. The study use pattern is summarized in Table B.3.1.

TABLE B.3.1. Use Pattern Information.		
Chemical name	[cyclohexane-2-^{14}C]mesotrione and [phenyl-U-^{14}C]mesotrione	
Application method	Test substances solubilized with ACN and formulated as FlC formulations. Applied to soil using a custom-made backpack sprayer.	
Application rate	CY label 0.29 lb ai/A (327 g ai/ha) 0.75 lb ai/A (836 g ai/ha)	PH label 0.27 lb ai/A (305 g ai/ha) 0.71 lb ai/A (796 g ai/ha)
Number of applications	1	
Timing of applications	Preemergence	
Pre-harvest interval (PHI)	50% Mature foliage: 90 days (both labels) Mature hay and peanuts: 154 days for CY label and 153 days for PH label	

B.4. Identification/Characterization of Residues

B.4.1. Sample Handling and Preparation

Samples of peanut foliage were collected at 50% mature harvest, and samples of peanut hay and peanuts were collected at maturity. Samples were stored frozen at the field site at -20 to 6°C, and were shipped frozen via ACDS freezer truck or on dry ice via FedEx to the first analytical facility (Syngenta Vero Beach Research Center, VBRC; Vero Beach, FL) within 2-20 days of harvest. At VBRC, samples were stored frozen (-31 to 11°C). Peanuts were rinsed in tap water to remove attached soil, separated by hand into nutmeats and hulls, homogenized in the presence of dry ice, and radioassayed. Processed samples were shipped frozen to Syngenta Crop Protection (Greensboro, NC) for metabolite characterization and identification; only the high-rate samples were shipped from the CY-label study. At Greensboro, samples were stored frozen (~-20°C), and extracts were either stored frozen or refrigerated (2-5°C).

Samples of **peanut foliage, hay, and hulls** following application of **CY-labeled mesotrione** at 0.75 lb ai/A were extracted ≥3x with ACN:water (8:2, v:v), then centrifuged and/or vacuum filtered. The extracts from foliage were separately subjected to C18 SPE to remove nonpolar endogenous material. Following elution of the extracts, the cartridge was rinsed with additional ACN/water, methanol, and/or chloroform. Peanut hay extracts were combined and subjected to C18 SPE as described for foliage. The resulting eluates for each matrix were combined, concentrated, and reserved for anion-exchange chromatography. The extracts of peanut hulls were simply combined and reserved for anion-exchange chromatography.

Anion-exchange chromatography was conducted using DEAE Sephadex A-25 resin. Eluates were dissolved in water, adjusted to pH 7, and applied to the column. Fractions were collected in 5-mL increments across a linear gradient of water to 1.0 M potassium bromide. Residues were characterized as neutral/base (early eluting), neutral/acidic, and/or acidic. Based on the submitted flow charts, anion-exchange separation was concluded with an ethanol wash. Vials containing relevant peaks were combined and purified using C18 SPE. Residues were eluted with water, followed by ACN, and methanol if needed. The ACN phases of the neutral/base and selected acid peaks were profiled using reverse-phase HPLC.

Samples of **peanut foliage, hay, and hulls** following application of **PH-labeled mesotrione** (both rates) were extracted 4x with ACN:water (8:2, v:v), then filtered. The extracts were combined and applied to a C18 SPE column with water; the resulting eluates were concentrated to an aqueous fraction and reserved for TLC and/or HPLC analysis. Following elution of the extracts for foliage and hay, the C18 cartridge was eluted with additional ACN and methanol. The resulting eluates for each matrix were combined, and the combined organic phase was reserved for HPLC and/or TLC analysis and/or subjected to acid hydrolysis with 6 N HCl at reflux. The acid hydrolysate was purified on an XAD-7 column. Residues were eluted with water, methanol (high-rate hay only), 40% ACN, and 80% ACN. The ACN and methanol phases (high-rate hay) were combined and reserved for HPLC chromatography. For peanut hulls, the extract following C18 elution was concentrated and partitioned 3x with chloroform. The aqueous phase was reserved for HPLC analysis and/or acid hydrolysis with 6 N HCl as described above for foliage and hay.

The nonextractable residues of **50% mature foliage, hay, hulls, and nutmeats** from the **PH-label study** (both rates) were refluxed overnight with water. The water-soluble fraction, designated polysaccharides, was reserved for HPLC analysis. The remaining nonextractable residues were subjected to base hydrolysis with 10% NaOH at reflux overnight; resulting solids were characterized as cellulose. The hydrolysate was adjusted to pH 1 with HCl and filtered. The resulting solids were designated as lignin. The filtrate was partitioned with DCM, and the organic (low-rate nutmeats only) and aqueous phases were reserved for HPLC analysis. Separate aliquots of the nonextractable residues of high-rate matrices were hydrolyzed with 6 N HCl at reflux and filtered. The hydrolysate was applied to an XAD-7 column, and residues were eluted with water, 40% ACN, and 80% ACN. The ACN eluates were combined, and the water and ACN eluates were reserved for HPLC.

Samples of **peanut nutmeat** following application of **CY-labeled mesotrione** at 0.75 lb ai/A were subjected to two separate extraction procedures. In the first extraction procedure, intended to resolve polar residues, nutmeats were extracted 3x with ACN:water (8:2, v:v) followed by ethyl acetate. The first two ACN/water extracts were combined and subjected to C18 SPE to remove nonpolar materials; residues were eluted with ethyl acetate. The resulting ethyl acetate phase was not further analyzed, but the ACN/water phase was further separated by C18 SPE into aqueous and organic fractions. The organic fraction was reserved for reverse-phase HPLC chromatography.

In the second extraction procedure, intended to resolve nonpolar residues, nutmeats were sequentially extracted with hexane, hexane:ethyl acetate (1:1, v:v), ethyl acetate, and ACN:water (8:2, v:v; 2x). Samples were filtered after each extraction step. The hexane, hexane/ethyl acetate, and ethyl acetate extracts, containing peanut oil, were combined and concentrated to an oily residue, then dissolved in hexane and chloroform, and applied to an amino SPE cartridge. Residues were sequentially eluted with chloroform:2-propanol (2:1, v:v), 2% acetic acid in diethyl ether, and methanol; the eluates were collected separately, and were designated the neutral lipid, fatty acid, and phospholipid fractions, respectively. The neutral lipid fraction was reserved for HPLC analysis. The peanut oil fraction was also base hydrolyzed by heating with methanol/potassium hydroxide/toluene (at 80°C for 80 minutes). The resulting hydrolysate was acidified to pH 1 with 12 N HCl, then partitioned with hexane. Subsamples of the peanut oil, before and after base hydrolysis were reserved for HPLC analysis.

Samples of **peanut nutmeat** following application of **PH-labeled mesotrione** (both rates) were extracted with hexane (2x) followed by ACN:water (8:2, v:v; 2x). The hexane extracts from both rates were respectively combined. The ACN/water extracts from the low-rate were not further investigated. The ACN/water extracts from the high rate were combined and partitioned with hexane; the ACN/water phase was reserved for HPLC analysis, and the resulting hexane phase was combined with the initial hexane extracts. The combined hexane extracts from both rates were reserved for HPLC analysis or subjected to base hydrolysis with 1 N KOH at reflux for 6 hours. The hydrolysate was adjusted to pH 2 with acetic acid and partitioned 2x with DCM. The resulting aqueous phase was not further investigated; an aliquot of the organic phase (high rate only) was reserved for HPLC analysis, and an aliquot (both rates) was subjected to acid hydrolysis with 6 N HCl at reflux for 4 hours, basified with ammonium hydroxide, and partitioned with DCM. The resulting aqueous phase did not contain detectable radioactivity; the organic phase was reserved for HPLC analysis. An aliquot of the organic phase from the high rate was separated into two fractions, 67A and 67B via preparative HPLC; each fraction was refluxed with 1 N KOH for 24 hours, adjusted to pH 2 with acetic acid, and partitioned with DCM 2x. The resulting organic phases were reserved for HPLC analysis.

An aliquot of the combined PH-label hexane extracts from each rate was also subjected to further procedures to characterize nonpolar residues. The residues were eluted through an amino SPE column to produce neutral lipid, fatty acid, and phospholipid fractions as described above for CY label peanut oil. The neutral lipids fraction was applied to a second amino SPE column, and residues were eluted with hexane (cholesterol ester fraction), 1% diethyl ether and 10% DCM in hexane (triacylglycerol fraction), 5% ethyl acetate in hexane (cholesterol fraction), 15% ethyl

acetate in hexane (diacylglycerol fraction), and chloroform:methanol (2:1, v:v; monoacylglycerol fraction). The triacylglycerol fraction was subjected to acid hydrolysis with 6 N HCl at reflux, and the hydrolysate was partitioned with DCM. The resulting organic fraction was reserved for HPLC analysis.

A separate subsample of PH-label nutmeat (high rate) was extracted with hexane (2x), and separate aliquots of the combined hexane extracts were subjected to (i) enzyme hydrolysis with lipase, esterase, and pancreatin; (ii) enzyme hydrolysis with cellulase and β-glucosidase; or (iii) aminolysis with diethylamine. Enzyme hydrolyses were conducted at 42 or 47 °C for ~24 hours using TRIS-HCl buffer, pH 7.8-8 (solution of esterase, lipase, and pancreatin), or sodium acetate buffer solution, pH 4.6 (cellulase and glucosidase). Aminolysis was conducted at 52 °C for 6 hours. The resulting hydrolysates/extracts were partitioned with DCM (2x), and the organic phases were reserved for HPLC analysis.

To further characterize residues in peanuts in the **CY-label study, auxiliary *in vitro* metabolism experiments** were conducted using both excised plants at the 1st true-leaf stage and cell cultures. The excised plants were extracted 2x with ACN:water, and the extracts were combined, concentrated, and subjected to preparative HPLC. Peanut cell cultures were subjected to C18 SPE; residues were sequentially eluted with two aliquots each of water, ACN, and methanol. The first ACN aliquot was subjected to preparative HPLC and reserved for HPLC, nuclear-magnetic resonance (NMR), MS, and TLC analyses.

B.4.2. Analytical Methodology

TRR in duplicate or triplicate aliquots of samples and nonextractable residues were determined by combustion/LSC; TRR in extracts were determined directly by LSC. The reported limit of quantitation (LOQ) for TRR determinations was 0.002 ppm for peanut matrices.

The ACN phases of the neutral/base and acidic regions of CY label 50% mature foliage, hay, and hulls were profiled by HPLC analyses. HPLC analysis was also used in both studies for quantitation of residues via fraction collection and for further characterization/identification of residues in peanut matrices via co-chromatography and comparison of metabolite profiles. Two reverse-phase HPLC systems were used in the CY-label study, both equipped with variable-wavelength UV detectors, radioisotope flow monitors (β-Ram detectors), and fraction collectors. The first system used a polymeric reverse-phase column (PLRP-S), UV detection at 235 nm, and a gradient mobile phase of 0.1% acetic acid, ACN, and methanol. The second system used a C18 column, UV detection at 235 nm, and a gradient mobile phase of methanol and ethyl acetate. Three HPLC systems were used in the PH-label study. The first system was the same as the first system described above, and the second system differed only in the use of a C8 column. The third HPLC system used a C-18 column and a gradient mobile phase of 0.1% acetic acid and tetrahydrofuran/ACN. Metabolites MNBA, AMBA, MBA, and 4-OH-mesotrione, as well as fatty acids were identified/characterized by co-chromatography and/or retention time comparisons with nonlabeled and radiolabeled reference standards. Chemical names and structures for the reference standards are presented in Appendix I.

In the CY-label study, one-dimensional TLC analysis was used to characterize residues in excised peanut plants and peanut cell cultures in the auxiliary *in vitro* metabolism experiments. TLC analyses were conducted using silica gel 60 F-254 plates and solvent systems of ethyl acetate:n-propanol:water:acetic acid (64:22:12:2, v:v:v:v) and methyl ethyl ketone:ACN:acetic acid:water (80:16:4:6, v:v:v:v). Radioactivity was detected by radioanalytic imaging or phosphorimaging, and nonradiolabeled standards were detected by UV light (254 nm). In the PH-label study, one-dimensional TLC analysis was used to characterize and identify metabolites in the aqueous fraction and combined organic fractions of foliage following C18 SPE. Analyses were conducted using silica-gel plates and a solvent system of chloroform:methanol:formic acid:water (75:25:4:2). Metabolites were isolated from the plates using ACN:water (9:1, v:v), and the resulting extracts was filtered and concentrated for further analysis as necessary. Radioactivity was detected using radioanalytic imaging.

Isolated peaks from the excised peanut plants and cell cultures in the CY-label study were analyzed by GC/MS or LC/MS conducted on systems equipped with quadrupole mass spectrometers operated in both positive and negative ion modes. The first system (GC/MS) was equipped with a direct capillary GC inlet and fused silica capillary columns and used electron ionization and chemical ionization. The second system (LC/MS) was equipped with an atmospheric-ionization interface, a UV detector, and a radioisotope flow monitor.

C. RESULTS AND DISCUSSION

The storage conditions and intervals for peanut samples are presented in Table C.1. The petitioner provided critical sample handling and storage dates for all samples. In the CY-label study, initial profiling of all matrices and characterization of the polar metabolites in nutmeats (first extraction) was completed within 94-115 days (~3-4 months) of harvest; characterization of nonpolar residues in peanut nutmeats (second extraction) was initiated within 184 days (6.1 months) of harvest and completed within 323 days (10.6 months). Characterization of residues was completed within 219 days (7.2 months) of harvest for 50% mature foliage, and within 129-143 days (4.2-4.7 months) of harvest for hay and hulls; quantitation of residues was completed within 129-272 days (4.2-8.9 months) for foliage, hay, and hulls. In the PH-label study, sample analysis was completed within 185 days (6.1 months) for 50% mature foliage, 325 days (10.7 months) for hay, 176 days (5.8 months) for hulls, and 585 days (19.2 months) for nutmeats.

To support storage conditions and intervals of samples and extracts, additional storage stability analyses were conducted in both the CY- and PH-label studies. In the CY-label study, the petitioner re-extracted and analyzed samples of 50% mature foliage and hay 311 and 267 days, respectively, after harvest, and compared the results with those of 50% mature foliage from initial profiling (analyzed 115 days after harvest) and hay from the samples analyzed for characterization and quantitation of residues (analyzed 129 days after harvest). In the PH-label study, to support sample storage conditions and intervals of samples, the petitioner re-extracted, partitioned, and analyzed samples of low-rate 50% mature foliage 437-442 days after harvest and samples of high-rate nutmeat 597 days after harvest. The results were compared with those of foliage from initial profiling (analyzed 182-185 days after harvest) and the original hexane extraction of high-rate nutmeat (analyzed 331 days after harvest). To demonstrate the stability of

the extracts on storage, petitioner re-analyzed the organic and aqueous phases and compared the HPLC profiles following storage of the extracts for 422-442 days (~14-15 months) for low-rate hay, hulls, and nutmeat (hexane extract only) and high-rate hulls; 235-256 days (~8 months) for foliage (both rates); and 202-209 days (~7 months) for high-rate hay. The data indicated that there were no significant changes in the metabolite profile following storage for either RACs or extracts. The submitted storage stability data are adequate to support the peanut metabolism study. Although no storage stability data were submitted for hulls (RAC), no additional data are required because initial profiling and characterization in the CY-label study were completed within 6 months of harvest, and analyses in the PH-label study were completed within 6 months.

Samples of peanut foliage were collected at 50% mature harvest 90 days after a single preemergence application of CY-labeled mesotrione at 0.29 or 0.75 lb ai/A or PH-labeled mesotrione at 0.27 or 0.71 lb ai/A; samples of mature peanut hay and peanuts were collected 153-154 days after application.

TRR in peanut matrices were determined by combustion/LSC; TRR are reported in Table C.2.1. Following application of CY-labeled mesotrione at 0.29 lb ai/A, TRR were 0.006 ppm in 50% mature foliage, 0.004 ppm in hay, and 0.005 and 0.007 ppm in hulls and nutmeats, respectively. Following application at 0.75 lb ai/A, TRR were 0.020 ppm in foliage, 0.011 ppm in hay, and 0.015 and 0.022 ppm in hulls and nutmeats, respectively. Following application of PH-labeled mesotrione at 0.27 lb ai/A, TRR were 0.028 ppm in 50% mature foliage, 0.012 ppm in hay, and 0.011 and 0.013 ppm in hulls and nutmeats, respectively. Following application at 0.71 lb ai/A, TRR were 0.064 ppm in foliage, 0.028 ppm in hay, and 0.025 and 0.037 ppm in hulls and nutmeats, respectively. In the CY-label study, only samples from the high rate were subjected to further extraction and analysis for characterization of residues.

The distribution of the radioactivity in peanut matrices is presented in Tables C.2.2.1 (CY label, high rate), C.2.2.2 (PH label, low-rate), and C.2.2.3 (PH label, high rate). In the CY-label study, solvent extraction with ACN/water released ~43%, 27%, and 20% TRR in 50% mature foliage, hay, and hulls respectively. No further attempts were made to release radioactivity from these matrices; nonextractable residues were 65.9-84.5% TRR (0.008-0.013 ppm). Nutmeats were subjected to two separate extraction procedures intended to resolve polar and nonpolar residues. In the first procedure, extraction with ACN/water and ethyl acetate released 43.5% TRR (0.012 ppm); in the second procedure, extraction with hexane and ethyl acetate released 51.4% TRR (0.011 ppm). Nonextractable residues in nutmeat, accounting for 50.8% TRR (~0.011 ppm), were not further investigated. Although nonextractable residues accounting for ≥50% TRR in all matrices were not further investigated, HED concludes that the extraction procedures were adequate because TRR were low in all peanut matrices, and metabolism of mesotrione appeared to be extensive. Residues were identified and quantitated by HPLC following further characterization via anion-exchange chromatography or SPE on an amino column (for nutmeats).

In the PH-label study, solvent extraction with ACN/water released ~41-42%, 32-34%, and 20-23% TRR in low- and high-rate 50% mature foliage, hay, and hulls respectively. Additional radioactivity was released from the nonextractable residues by refluxing with water followed by acid and base hydrolysis. These procedures released ~27-52%, 41-42%, and 31-38% TRR in

low- and high-rate foliage, hay, and hulls. Remaining nonextractable residues, accounting for 13%, 26%, and 46% TRR (0.003-0.005 ppm) in low-rate foliage, hay, and hulls and for 26%, 24%, and 20% TRR (0.005-0.016 ppm) in high-rate foliage, hay, and hulls, were characterized as cellulose or lignins on the basis of base and acid hydrolysis. For nutmeats, extraction with hexane released 36% and 32% TRR (0.005 and 0.012 ppm) in low- and high-rate samples, respectively. Additional radioactivity was released from the nonextractable residues by refluxing with water followed by acid and base hydrolysis. These procedures released ~92% TRR in low-rate nutmeats and ~29% TRR in high-rate nutmeats; remaining nonextractable residues, accounting for 16% TRR in low-rate nutmeats and 50% TRR (0.018 ppm) in high-rate nutmeats, were characterized as cellulose or lignin. The extraction procedures for the PH-label study were adequate. Residues were identified and quantitated by HPLC and identification of metabolites was confirmed by TLC co-chromatography.

Accountabilities, based on extraction procedures ranged 100-107% for the CY-label study. In the PH-label study, accountabilities ranged 92-114% for low- and high-rate foliage and hay, low-rate hulls, and high-rate nutmeats; accountabilities of 76% and 146% were obtained for high-rate hulls and low-rate nutmeats, respectively. The petitioner made no attempt to explain the low recovery observed for high-rate hulls or the excessively high recovery obtained for low-rate nutmeats, which resulted from high reported TRR in the aqueous and organic phases following DCM partitioning of the acidified hydrolysate of the nonextractable residues. HED furthermore notes, that the petitioner did not address the loss of radioactivity on further characterization/identification analysis following extraction procedures and did not provide quantitative data for minor unknowns for any fraction except the aqueous fraction following initial partitioning of the ACN/water phase.

The characterization and identification of residues in peanut matrices is summarized in Tables C.2.3.1 (CY label, high rate), C.2.3.2 (PH label, low-rate), and C.2.3.3 (PH label, high rate). Mesotrione was not identified in any peanut matrix following preemergence application of CY-labeled mesotrione. The only identified metabolite was 4-OH-mesotrione, at 1.6% and 1.4% TRR in 50% mature foliage and hay, respectively, and 0.5% TRR in hulls. Identification of this metabolite was adequately confirmed by LC/MS and a number of additional procedures. Minor unknowns (none present at ≥0.001 ppm in any matrix) accounted for 15.1%, 6.0%, and 3.3% TRR in foliage, hay, and hulls, and remaining radioactivity was characterized on the basis of anion-exchange chromatography (as neutral/basic, neutral/acidic, or acidic) and distribution into organic solvents (including ACN, methanol, and ethanol) or aqueous phases. In peanut nutmeats, the distribution of polar residues was similar to that in the other matrices. Nonpolar residues in nutmeats were characterized as neutral lipids (37.8% TRR, 0.008 ppm), fatty acids (5.7% TRR, 0.001 ppm), and phospholipids (4.1% TRR, 0.001 ppm) on the basis of elution characteristics on amino SPE. The petitioner confirmed the presence of fatty acids via additional characterization procedures using radiolabeled standards of glycerol and triacylglycerides labeled in the fatty acid portion of the molecule.

The metabolite profile following preemergence application of PH-labeled mesotrione differed from the profile observed in the CY-label study. Although mesotrione was not identified in any matrix from either treatment rate, metabolites MNBA and AMBA were identified in all matrices,

MBA was identified in foliage, hay, and nutmeat, and 4-OH-mesotrione was identified in nutmeat only. MNBA accounted for 12.4% TRR (0.003 ppm), 5.1% TRR (0.001 ppm), and 3.6% TRR (<0.001 ppm) in low-rate foliage, hay, and hulls, respectively, and was not identified in low-rate nutmeat. In high-rate matrices, MNBA accounted for 11.1% TRR (0.007 ppm), 6.4% TRR (0.002 ppm), 9.6% TRR (0.002 ppm), and 2.4% TRR (0.001 ppm) in high-rate foliage, hay, hulls, and nutmeat, respectively. AMBA was identified in all matrices treated at low and high rates, respectively, at 16.7% and 7.1% TRR (0.005 ppm each) in foliage, 6.9% and 4.6% TRR (0.001 ppm each) in hay, 1.6% and 1.4% TRR (<0.001 ppm each) in hulls, and 15.0% and 1.4% TRR (0.002 and 0.001 ppm) in nutmeats. MBA was identified at 0.6% TRR (<0.001 ppm) in high-rate foliage, 3.2% and 2.8% TRR (<0.001 ppm each), respectively, in low- and high-rate hay, and at 6.7% TRR (0.001 ppm) in low-rate nutmeat. 4-OH-Mesotrione was identified in low-rate nutmeat at 6.9% TRR (0.001 ppm). Additional residues were characterized as cellulose and lignins on the basis of hydrolysis in all matrices as noted above, and, as in the CY-label studies, residues in low- and high-rate nutmeats were characterized as neutral lipids, fatty acids, and phospholipids on the basis of elution characteristics on amino SPE; the neutral lipid residues were further characterized on a second amino SPE column. Based on these analyses, residues in low- and high-rate nutmeats, respectively, were characterized as cholesterol esters (12.8% and 2.7% TRR), triacylglycerols (17.4% and 23.5% TRR), and monoacylglycerols (7.0% and 7.3% TRR), fatty acids (4.7% and 6.5% TRR), and phospholipids (7.0% TRR and trace). One major polar unknown, Peak 1, was found in all matrices from low- and high-rate treatments, respectively, at 17.6% and 11.2% TRR in foliage, 13.1% and 32.1% TRR in hay, 8.6% and 12.4% TRR in hulls, and 14.0% and 7.0% TRR in nutmeat. Peak 1 is believed to consist of AMBA conjugates (see discussion below). Discrete unknowns (identified on the basis of fraction collection by vial numbers) accounted for 1.9-11.4% TRR (≤0.003 ppm) in low- and high-rate foliage, hay, and hulls, and low-rate nutmeat, and minor unknowns (none present at ≥0.001 ppm in any matrix) accounted for at least 1.0-1.6% TRR in foliage, hay, and hulls from both rates. Remaining radioactivity was characterized on the basis of distribution into organic solvents (including ACN, methanol, and ethanol) or aqueous phases.

In the CY-label study, to confirm identification of 4-OH-mesotrione (HPLC Peak 7), which was found in all peanut matrices, the petitioner compared the chromatographic profile of 50% mature foliage with those for excised plants and cell cultures from the *in vitro* studies. The largest portion of the applied radioactivity (61%) in excised plants corresponded to Peak 7, which was found to co-chromatograph on HPLC and 1-D TLC analysis with 4-hydroxy mesotrione and with Peaks 6 and 7 from 50% mature foliage. Peak 7 was further purified on an anion-exchange column followed by C18 SPE. The resulting organic fraction was profiled by HPLC and analyzed by MS, which further confirmed identification of 4-OH-mesotrione. HPLC, TLC, NMR and MS analysis of Peak 7 isolated from cell cultures also confirmed identification of 4-OH-mesotrione.

The incorporation of radiolabeled CO_2 into natural products in peanut nutmeats was further investigated in the CY-label study by comparing chromatographic results from the second extraction to those for radiolabeled standards of glycerol and triacylglycerides (labeled in the fatty acid portion of the molecule) that had been spiked into purchased peanut oil and base hydrolyzed using the same procedure. The retention times were similar to those for

triacylglycerols. The petitioner concluded that the comparison of base-hydrolyzed oil and base-hydrolyzed ^{14}C-triacylglyceride standards indicated that the data were consistent with the metabolism of mesotrione into small moieties that incorporate the radiolabel in lipid biosynthesis. The peanut oil fraction was characterized as primarily neutral lipids with the radiolabel incorporated into the fatty acid portion of the lipids.

In the PH-label study, HPLC analysis of the organic fraction in foliage, hay, and hulls (both rates) following partitioning of the ACN/water extract resulted in a large hump of radioactivity that was identified as the Blue zone. Acid hydrolysis of the Blue zone with 6 N HCl released AMBA (identified by HPLC co-chromatography with radiolabled reference standard), suggesting the presence of AMBA conjugates.

To further characterize residues in Peak 1 in the PH-label study, the aqueous phase of hulls (both rates) was subjected to acid hydrolysis followed by separation on an XAD-7 column as described for the organic fractions above. On HPLC analysis of the resulting aqueous and organic phases, Peak 1 was reduced from 5.4% to 3.0% TRR in low-rate hulls, and from 7.0% to 3.4% TRR in high-rate hulls. MNBA was identified at 0.6% TRR in low-rate hulls and 1.1% TRR in high-rate hulls, and the majority of the radioactivity was characterized as discrete unknowns in vials 30-37 and 38-50 (low-rate) and 40-47 (high rate). The petitioner noted that in the confined rotational crop study that was previously reviewed (see Memo, S. Levy, 06-JUN-2001; DP#: 245477), this area was believed to consist of numerous AMBA conjugates or AMBA sulfate conjugates which are further conjugated at the carboxyl group. The petitioner states that this linkage is very stable in some conjugates, therefore explaining why Peak 1 did not completely cleave to AMBA with acid hydrolysis.

In the PH-label study, enzyme hydrolysis of the hexane extract of high-rate nutmeats with lipase, esterase, and pancreatin released ~8% TRR to components less polar than the initial profile; hydrolysis with cellulase and glucosidase, and aminolysis with diethylamine did not change the HPLC profile appreciably. Based on characterization of high-rate nutmeats, the petitioner concluded that the hexane extract contains a mixture of acylglycerides that have probably incorporated MNBA or AMBA.

C.1. Storage Stability

Samples of 50% mature foliage, hay, hulls, and nutmeats were stored frozen (~-20°C) prior to HPLC profiling and analysis. The petitioner provided critical sample handling and storage dates for all samples. In the CY-label study, initial profiling of all matrices and characterization of the polar metabolites in nutmeats (first extraction) was completed within 94-115 days (~3-4 months) of harvest; characterization of nonpolar residues in peanut nutmeats (second extraction) was initiated within 184 days (6.1 months) of harvest and completed within 323 days (10.6 months). Characterization of residues was completed within 219 days (7.2 months) of harvest for foliage, and within 129-143 days (4.2-4.7 months) of harvest for hay and hulls; quantitation of residues was completed within 129-272 days (4.2-8.9 months) for 50% mature foliage, hay, and hulls. In the PH-label study, sample analysis was completed within 185 days (6.1 months) for 50% mature

foliage, 325 days (10.7 months) for hay, 176 days (5.8 months) for hulls, and 585 days (19.2 months) for nutmeats.

To support storage conditions and intervals of samples from the CY-label study, the petitioner re-extracted and analyzed samples of 50% mature foliage and hay 311 and 267 days, respectively, after harvest, and compared the results with those of foliage from initial profiling (analyzed 115 days after harvest) and hay from the samples analyzed for characterization and quantitation of residues (analyzed 129 days after harvest). When extractability of residues into ACN/water, elution through C18 SPE and distribution into aqueous and organic fractions, and distribution of individual peaks on HPLC analysis were compared, no significant differences in any of the factors were observed for 50% mature foliage following extended storage. Results were comparable for stored hay for extractability and C18 SPE analysis; however, whereas the majority of radioactivity was found in early eluting peaks (6 peaks) on HPLC analysis of the hay sample used for quantitation and characterization, radioactivity was evenly distributed over a broad range of minor peaks (11 peaks) in the stored sample. Because each individual peak for both samples represented <0.001 ppm, HED does not consider this difference to be significant

To support sample storage conditions and intervals from the PH-label study, the petitioner re-extracted, partitioned, and analyzed samples of low-rate 50% mature foliage 437-442 days after harvest and samples of high-rate nutmeat 597 days after harvest. The results were compared with those of foliage from initial profiling (analyzed 182-185 days after harvest) and the original hexane extraction of high-rate nutmeat (analyzed 331 days after harvest). When extractability of residues into ACN/water, elution through C18 SPE and distribution into aqueous and organic fractions, TLC profile, and distribution of individual peaks on HPLC analysis were compared, no significant differences in any of the factors were observed for foliage or nutmeats following extended storage. To demonstrate the stability of the extracts on storage, petitioner re-analyzed the organic and aqueous phases and compared the HPLC profiles following storage of the extracts for 422-442 days (~14-15 months) for low-rate hay, hulls, and nutmeat (hexane extract only) and high-rate hulls; 235-256 days (~8 months) for foliage (both rates); and 202-209 days (~7 months) for high-rate hay. No significant changes were observed in either the aqueous or organic profiles for any of the matrices.

The submitted storage stability data are adequate to support the peanut metabolism studies. Although no storage stability data were submitted for hulls (RAC), no additional data are required because initial profiling and characterization in the CY-label study were completed within 6 months of harvest and analyses in the PH-label study were completed within 6 months.

TABLE C.1. Summary of Storage Conditions.				
Matrix[1]		Storage Temperature (°C)	Actual Storage Duration[2]	Interval of Demonstrated Storage Stability
CY Label				
Foliage, 50% mature		-20	115-219 days (3.8-7.2 months)	311 days (10.2 months)
Hay		-20	94-272 days (3.1-8.9 months)	267 days (8.8 months)
Hulls		-20	98-255 days (2.3-8.4 months)	None demonstrated for the RAC
Nutmeats (first extraction)		-20	99 days (3.3 months)	597 days (19.6 months; PH data)
Nutmeats (second extraction)	RAC	-20	184-323 days (6.1-10.6 months)	597 days (19.6 months; PH data)
	Extract	2-5	85-224 days (2.8-7.4 months)	422 days (13.9 months; PH data)
PH Label				
Foliage, 50% mature		-20	178-185 days (5.9-6.1 months)	RAC: 437-442 days (14.4-14.5 months) Extracts: 235-256 days (7.7-8.4 months)
Hay	RAC	-20	176-325 days (5.8-10.7 months)	267 days (8.8 months; CY data)
	Org extract	2-5	183 days (6.0 months)	202-442 days (6.6-14.5 months)
Hulls		-20	176 days (5.8 months)	None demonstrated for the RAC; Extracts: 426-442 days (14-14.5 months)
Nutmeats	RAC	-20	189-585 days (6.2-19.2 months)	597 days (19.6 months)
	Extracts	2-5	156-410 days (5.1-13.5 months)	422 days (13.9 months)

[1] Extracts were stored for 2-36 days, except where noted.
[2] Interval from harvest to analysis.

C.2. Identification, Characterization, and Distribution of Residues

TABLE C.2.1. TRR in Peanut Matrices.							
Matrix	Timing and Applic. No.	CY Label			PH Label		
		PHI (days)	TRR, ppm		PHI (days)	TRR, ppm	
			0.29 lb ai/A	0.75 lb ai/A		0.27 lb ai/A	0.71 lb ai/A
Foliage, 50% mature	Single preemergence	90	0.006	0.020	90	0.028	0.064
Hay		154	0.004	0.011	153	0.012	0.028
Hulls		154	0.005	0.015	153	0.011	0.025
Nutmeats		154	0.007	0.022	153	0.013	0.037
Soil		154	0.013	0.035	153	≤0.001	0.003-0.011

TABLE C.2.2.1. Distribution of the Parent and the Metabolites in Peanut Matrices Following Application of [Cyclohexane-2-^{14}C]Mesotrione at 0.75 lb ai/A.[1]

Metabolite Fraction	50% Mature Foliage		Hay		Hulls		Nutmeat	
	TRR = 0.020 ppm		TRR = 0.011 ppm		TRR = 0.015 ppm		TRR = 0.022 ppm	
	%TRR	ppm	%TRR	ppm	%TRR	ppm	%TRR	ppm
ACN/water	38.9	0.008	28.2	0.003	19.9	0.003		
ACN/water (post-SPE)	43.2	0.009	27.4	0.003	--	--		
Neutral/base	11.7	0.003	6.7	0.001	4.4	0.001		
-Aqueous	5.6	0.001	2.1	<0.001	2.2	<0.001		
-ACN (subjected to HPLC)	5.3	0.001	3.9	<0.001	1.5	<0.001		
Unknowns <0.001 ppm[2]	5.4	0.001	3.8	<0.001	1.3	<0.001		
Unresolved ^{14}C	0.1	<0.001	0.4	<0.001	0.2	<0.001		
Neutral/acid					4.3	0.001		
Acidic (subjected to C18 SPE)	17.3	0.003	16.0	0.002	8.3	0.002		
-Aqueous	3.5	<0.001	3.8	<0.001	1.5	<0.001		
-ACN (subjected to HPLC)	11.6	0.002	4.1	<0.001	2.8	<0.001		
4-OH-mesotrione (Peak 7)	1.6	<0.001	1.4	<0.001	0.5	<0.001		
Unknowns <0.001 ppm[3]	9.7	0.002	2.2	<0.001	2.0	<0.001		
Unresolved ^{14}C	0.4	<0.001	0.6	<0.001	0.2	<0.001		
-ACN (not investigated)			5.5	<0.001				
-Methanol	2.1	<0.001	0.9	<0.001				
Acidic (not further investigated)	3.0	<0.001			4.6	0.001		
Ethanol wash	1.2	<0.001	1.4	<0.001	1.8	<0.001		
Nonextractable	65.9	0.013	71.6	0.008	84.5	0.013		
First extraction nutmeat								
ACN/water (subj. to C18 SPE)							6.4	0.003
ACN/water							7.3	0.002
-Aqueous							3.6	0.001
-Organic							5.3	0.001
Peak 7							1.4	<0.001
Unknowns <0.001 ppm[4]							3.6	0.001
Unresolved							0.1	<0.001
Ethyl acetate							4.8	0.001
ACN/water (not further investig'd)							2.8	0.001
Ethyl acetate							34.3	0.008
Nonextractable							NR	NR
Second extraction nutmeat								
Hexane and ethyl acetate							51.4	0.011
Neutral lipids							37.8	0.008
Fatty acids							5.7	0.001
Phospholipids							4.1	0.001
ACN/water							4.7	0.001
Unextractable							50.8	0.011

[1] Shading indicates that the extraction step and/or characterization analysis was not conducted for the matrix in question.
NR = Not reported

[2] Consisting of: ≥12 components, each ≤1.2% TRR in 50% mature foliage; ≥8 components, each ≤1.0% TRR in hay; and ≥7 components, each ≤0.5% TRR in hulls.
[3] Consisting of ≥11 components, each ≤1.4% TRR in 50% mature foliage, ≥7 components, each ≤0.5% TRR in hay; and ≥8 components, each ≤0.6% in hulls.
[4] Consisting of ≥10 components, each ≤0.9% TRR.

TABLE C.2.2.2. Distribution of the Parent and the Metabolites in Peanut Matrices Following Application of [Phenyl-U-^{14}C]Mesotrione at 0.27 lb ai/A.[1]

Metabolite Fraction	50% Mature Foliage		Hay		Hulls		Nutmeat	
	TRR = 0.028 ppm		TRR = 0.012 ppm		TRR = 0.011 ppm		TRR = 0.013 ppm	
	%TRR	ppm	%TRR	ppm	%TRR	ppm	%TRR	ppm
ACN/water	42.2	0.012	31.5	0.004	23.0	0.003		
ACN/water (post SPE)	43.5	0.012	25.2	0.003	22.1	0.002		
-Aqueous	23.6	0.007	16.0	0.002	15.5	0.002		
MNBA	10.9	0.003	4.0	0.001	2.4	<0.001		
AMBA	2.1	0.001	--	--	--	--		
Peak 1	4.5	0.001	4.0	0.001	5.4	0.001		
Vials 35-38/32-35/33-40	1.9	0.001	1.0	<0.001	3.0	<0.001		
Minor unknowns[2]	>1.6	<0.001	>1.0	<0.001	>1.4	<0.001		
-ACN	12.3	0.003	5.6	<0.001	--	--		
-Methanol	3.5	0.001	2.1	<0.001	--	--		
-Combined organic[3]	15.8	0.004	13.3	0.002	5.3	<0.001		
MNBA	0.1	<0.001	--	--				
Peak 1	0.3	<0.001	0.6	<0.001				
Blue zone (acid hydrolyzed)[4]	16.7	0.005	8.9	0.001				
-Aqueous	0.3	<0.001	0.4	<0.001				
-Combined ACN	12.3	0.003	10.3	0.001				
AMBA	4.9	0.001	2.2	<0.001				
Vials 37-45	--	--	1.9	<0.001				
(1) Nonextractable (water refluxed)	48.7	0.014	62.8	0.008	60.1	0.007	60.7[5]	0.008
Aqueous (polysaccharides)	29.3	0.008	12.3	0.002	8.7	0.001	14.0	<0.001
MNBA	0.6	<0.001	--	--			--	--
AMBA	7.2	0.002	2.2	<0.001			--	--
Peak 1	7.2	0.002	3.2	<0.001			5.0	<0.001
Vials 38-40	--	--	--	--	--	--	1.5	<0.001
Nonextractable (NaOH refluxed)	NR	NR	NR	NR	NR	NR	NR	NR
Solids (cellulose)	10.3	0.003	19.3	0.002	30.1	0.003	15.7	0.002
Hydrolysate (acidified)	NR	NR	NR	NR	NR	NR	NR	NR
Solids (lignins)	3.1	<0.001	6.3	<0.001	15.5	0.001	0.3	<0.001
Filtrate (partitioned)	NR	NR	NR	NR	NR	NR	NR	NR
-Aqueous	15.4	0.004	20.4	0.002	17.5	0.002	34.0	0.004
MNBA	0.8	<0.001	1.1	<0.001	1.2	<0.001	--	--
AMBA	2.5	0.001	2.5	<0.001	1.6	<0.001	6.0	0.001
MBA	--	--	3.2	<0.001	--	--	--	--
Peak 1	5.6	0.002	5.3	<0.001	3.2	<0.001	9.0	0.001
Vials 32-38/39-45	--	--	--	--	2.2	<0.001	2.7	<0.001
-DCM	7.6	0.002	8.1	0.001	5.0	<0.001	44.4	0.006

TABLE C.2.2.2. Distribution of the Parent and the Metabolites in Peanut Matrices Following Application of [Phenyl-U-^{14}C]Mesotrione at 0.27 lb ai/A.[1]

Metabolite Fraction	50% Mature Foliage		Hay		Hulls		Nutmeat	
	TRR = 0.028 ppm		TRR = 0.012 ppm		TRR = 0.011 ppm		TRR = 0.013 ppm	
	%TRR	ppm	%TRR	ppm	%TRR	ppm	%TRR	ppm
AMBA							9.0	0.001
MBA							6.7	0.001
4-OH-mesotrione							6.9	0.001
Vials 35-44							5.7	0.001
First extraction nutmeat								
Hexane (base hydrolyzed)							36.2	0.005
Aqueous							1.2	<0.001
Organic (acid hydrolyzed)							33.7	0.004
-Aqueous							trace	trace
-Organic							32.6	0.004
Vials 83-92							13.2	0.002
Vials 101-106							4.0	0.001
Vials 108-115							9.2	0.001
ACN/water							3.8	<0.001
Nonextractable							60.7	0.008
Second extraction nutmeat								
Hexane							36.2	0.005
Neutral lipids							36.1	0.005
Cholesterol ester							12.8	0.002
Triacylglycerols							17.4	0.002
-Aqueous							trace	trace
-DCM							13.8	0.002
Vials 101-106							1.8	<0.001
Vials 107-116							7.4	0.001
Cholesterol							trace	trace
Diacylglycerols							trace	trace
Monoacylglycerols							7.0	<0.001
Fatty acids							4.7	<0.001
Phospholipids							7.0	<0.001
ACN/water							3.8	<0.001
Unextractable							60.7	0.008

[1] Shading indicates that the extraction step and/or characterization analysis was not conducted for the matrix in question.
NR = Not reported
[2] Consisting of: ≥7 components, each ≤1.4 TRR in 50% mature foliage; and ≥5 components, each ≤0.70% TRR in hay.
[3] Consisting of ACN + methanol for foliage; ACN + methanol + SPE ACN wash (5.6% TRR, <0.001 ppm) for hay; and chloroform for hulls.
[4] Because the Blue zone comprised the majority of the radioactivity in the combined organic phase, the petitioner concluded that acid hydrolysis of the organic phase released residues in the Blue zone.
[5] See below for extraction procedures for nutmeat to this point

TABLE C.2.2.3. Distribution of the Parent and the Metabolites in Peanut Matrices Following Application of [Phenyl-U-^{14}C]Mesotrione at 0.71 lb ai/A.[1]

Metabolite Fraction	50% Mature Foliage		Hay		Hulls		Nutmeat	
	TRR = 0.064 ppm		TRR = 0.028 ppm		TRR = 0.025 ppm		TRR = 0.037 ppm	
	%TRR	ppm	%TRR	ppm	%TRR	ppm	%TRR	ppm
ACN/water	40.5	0.026	34.2	0.010	19.6	0.005		
ACN/water (post SPE)	37.5	0.024	31.4	0.009	18.9	0.005		
-Aqueous	19.2	0.012	24.8	0.007	18.2	0.005		
MNBA	10.7	0.007	5.8	0.002	1.7	<0.001		
AMBA	0.5	<0.001	1.1	<0.001	--	--		
MBA	--	--	1.1	<0.001	--	--		
Peak 1	4.4	0.003	7.6	0.002	6.7	0.002		
Vials 32-41	--	--	3.4	0.001	1.7	<0.001		
Vials 42-51	--	--	3.3	0.001	--	--		
Minor unknowns[2]	>1.3	>0.001	--	--	>1.6	<0.001		
-CAN	13.5	0.009	5.2	0.002	--	--		
-Methanol	2.1	0.001	3.6	0.001	--	--		
-Combined organic[3]	15.6	0.010	8.8	0.003	2.2	<0.001		
MNBA	0.4	<0.001	--	--	--	--		
Peak 1	1.3	0.001	0.2	<0.001	--	--		
Blue zone (acid hydrolyzed)[4]	14.8	0.010	5.3	0.002	--	--		
-Aqueous	0.7	<0.001	0.2	<0.001	--	--		
-Combined ACN (+ MeOH)	14.1	0.009	6.7	0.002	--	--		
AMBA	4.3	0.003	1.5	<0.001	--	--		
(1) Nonextractable (water refluxed)	59.6	0.038	67.7	0.019	68.5	0.017	61.5[5]	0.023
Aqueous (polysaccharides)	5.0	0.003	17.2	0.005	5.3	0.001	11.6	0.004
MNBA			0.6	<0.001			1.4	0.001
AMBA			2.0	0.001			0.8	0.001
MBA			1.7	<0.001			--	--
Peak 1			4.7	0.001			4.5	0.002
Nonextractable (NaOH refluxed)	NR	NR	NR	NR	NR	NR	NR	NR
Solids (cellulose)	23.4	0.015	21.1	0.006	19.6	0.005	43.8	0.016
Hydrolysate (acidified)	NR	NR	NR	NR	NR	NR	NR	NR
Solids (lignins)	2.2	0.001	2.9	<0.001	0.1	<0.001	6.0	0.002
Filtrate (partitioned)	NR	NR	NR	NR	NR	NR	NR	NR
-Aqueous	11.4	0.007	18.6	0.005	30.3	0.008	11.6	0.004
MNBA	--	--	--	--	7.9	0.002	1.0	<0.001
AMBA	0.6	<0.001	--	--	1.4	<0.001	0.6	<0.001
MBA	0.6	<0.001	--	--	--	--	--	--
Peak 1	5.5	0.003	19.6	0.005	5.7	0.001	2.5	0.001
Vials 37-48	--	--	--	--	9.7	0.003	--	--
-DCM	10.1	0.007	6.3	0.002	2.5	<0.001	5.8	0.002
AMBA	1.7	0.001						
Vials 110-116	1.0	0.001						
Vials 134-138	1.7	0.001						

TABLE C.2.2.3. Distribution of the Parent and the Metabolites in Peanut Matrices Following Application of [Phenyl-U-^{14}C]Mesotrione at 0.71 lb ai/A.[1]

Metabolite Fraction	50% Mature Foliage		Hay		Hulls		Nutmeat	
	TRR = 0.064 ppm		TRR = 0.028 ppm		TRR = 0.025 ppm		TRR = 0.037 ppm	
	%TRR	ppm	%TRR	ppm	%TRR	ppm	%TRR	ppm
(2) Nonextractable (acid hydrol.)	59.6	0.038	67.7	0.019	68.5	0.017	61.5	0.023
Hydrolysate	19.8	0.013	19.2	0.005	28.9	0.007	35.4	0.013
-Aqueous	11.5	0.007	10.1	0.003	16.2	0.004	32.9	0.012
MNBA	2.2	0.001	6.1	0.002	2.8	0.001	1.9	0.001
Peak 1	7.8	0.005	--	--	9.4	0.002	25.1	0.009
Vials 27-30	--	--	2.5	0.001	--	--	--	--
-Combined ACN	8.0	0.005	6.2	0.002	7.3	0.002	4.2	0.002
MNBA	1.0	0.001	1.0	<0.001	0.7	<0.001	0.5	<0.001
Peak 1	--	--	0.4	<0.001	1.0	<0.001	0.2	<0.001
Blue zone	2.2	0.001	3.4	0.001	3.8	0.001	2.2	0.001
Nonextractable	41.2	0.026	40.8	0.011	37.6	0.009	22.4	0.008
First extraction nutmeat								
Hexane (combined with Hexane 2)							26.8	0.010
ACN/water							NR	NR
-Hexane 2 (comb. with Hexane)							5.2	0.002
-Combined hexane (base hydrol.)							32.0	0.012
Aqueous							1.1	<0.001
Organic (acid hydrolyzed)							28.9	0.011
-Aqueous							trace	trace
-Organic							28.0	0.010
Vials 83-93 (67A)							11.5	0.004
Vials 101-107							3.3	0.001
Vials 108-114 (67B)							8.3	0.003
ACN/water							3.9	0.001
Peak 1							2.5	0.001
Nonextractable							61.5	0.023
Second extraction nutmeat								
Hexane (combined with Hexane 2)							26.8	0.010
ACN/water (partitioned)							NR	NR
-Hexane 2 (comb. with Hexane)							5.2	0.002
-Combined hexane (Amino SPE)							32.0	0.012
Neutral lipids (Amino SPE)							25.6	0.010
Cholesterol ester							2.7	0.001
Triacylglycerols (acid hydr.)							23.5	0.009
Aqueous							trace	trace
DCM							14.4	0.005
Vials 98-105							2.4	0.001
Vials 106-115							5.9	0.003
Cholesterol							trace	trace
Diacylglycerols							trace	trace
Monoacylglycerols							7.3	0.003

TABLE C.2.2.3. Distribution of the Parent and the Metabolites in Peanut Matrices Following Application of [Phenyl-U-^{14}C]Mesotrione at 0.71 lb ai/A.[1]

Metabolite Fraction	50% Mature Foliage		Hay		Hulls		Nutmeat	
	TRR = 0.064 ppm		TRR = 0.028 ppm		TRR = 0.025 ppm		TRR = 0.037 ppm	
	%TRR	ppm	%TRR	ppm	%TRR	ppm	%TRR	ppm
Fatty acids							6.5	0.002
Phospholipids							trace	trace
-ACN/water							3.9	0.001
Unextractable							61.5	0.023
Third extraction nutmeat								
Hexane (aliquots 1-3)							30.6	0011
(1) Lipase, esterase, pancreatin							NR	NR
Vials 82-96							4.4	0.002
Vials 98-105							4.0	0.001
Vials 106-118							25.3	0.009
(2) Cellulase, glucosidase							NR	NR
Vials 105-119							29.4	0.011
(3) Diethylamine							NR	NR
Vials 107-110							5.3	0.002
Vials 111-123							21.4	0.008
ACN/water							4.2	0.002
MNBA							0.2	<0.001
Peak 1							2.7	0.001
Nonextractable							58.7	0.022

[1] Shading indicates that the extraction step and/or characterization analysis was not conducted for the matrix in question.
NR = Not reported.
[2] Consisting of: ≥8 components, each ≤1.2 TRR in 50% mature foliage; and ≥4 components, each ≤1.4% TRR in hulls.
[3] Consisting of ACN + methanol for foliage and hay; and chloroform for hulls.
[4] Because the Blue zone comprised the majority of the radioactivity in the combined organic phase, the petitioner concluded that acid hydrolysis of the organic fraction released residues in the Blue zone.
[5] See below for extraction procedures for nutmeat to this point.

TABLE C.2.3.1. Summary of Characterization and Identification of Radioactive Residues in Peanut Matrices Following Application of [Cyclohexane-2-^{14}C]Mesotrione at 0.75 lb ai/A.[1]

Compound	50 % Mature Foliage		Hay		Hulls		Nutmeat	
	TRR = 0.020 ppm		TRR = 0.011 ppm		TRR = 0.015 ppm		TRR = 0.022 ppm	
	% TRR	ppm	% TRR	ppm	% TRR	ppm	% TRR	ppm
4-OH-Mesotrione	1.6	<0.001	1.4	<0.001	0.5	<0.001	--	--
Neutral lipids	--	--	--	--	--	--	37.8	0.008
Fatty acids	--	--	--	--	--	--	5.7	0.001
Phospholipids	--	--	--	--	--	--	4.1	0.001
Minor unknowns <0.001 ppm [2]	15.1	0.003	6.0	0.001	3.3	<0.001	--	--
Unresolved ^{14}C	0.5	<0.001	1.0	<0.001	0.4	<0.001	--	--
Aqueous neutral/base	5.6	0.001	2.1	<0.001	2.2	<0.001	--	--
Aqueous acidic	3.5	<0.001	3.8	<0.001	1.5	<0.001	--	--
ACN acidic	--	--	5.5	<0.001	--	--	--	--
Neutral/acidic components	--	--	--	--	4.3	0.001	--	--
Acidic components	3.0	<0.001	--	--	4.6	0.001	--	--
Methanol soluble	2.1	<0.001	0.9	<<0.001	--	--	--	--
Ethanol soluble	1.2	<0.001	1.4	<0.001	1.8	<0.001	--	--
ACN/water	--	--	--	--	--	--	4.7	0.001
Total identified	1.6	<0.001	1.4	<0.001	0.5	<0.001	--	--
Total characterized	31.0	0.006	20.7	0.002	18.1	0.003	52.3	0.012
Total extractable	38.9	0.008	28.2	0.003	19.9	0.003	51.4	0.011
Unextractable (PES)[3]	65.9	0.013	71.6	0.008	84.5	0.013	50.8	0.011
Accountability [4]	105		100		107		100	

[1] The petitioner did not correct values for loss on further characterization/identification analysis (e.g., anion-exchange chromatography); therefore, the sum of identified and characterized residues may not correspond to the reported total extractable residues.

[2] See Table C.2.2 for distribution of unknowns.

[3] Residues remaining after extractions.

[4] Accountability = (Total extractable + Total unextractable)/(TRR from combustion analysis; see TABLE C.2.1) * 100.

TABLE C.2.3.2. Summary of Characterization and Identification of Radioactive Residues in Peanut Matrices Following Application of [Phenyl-U-^{14}C]Mesotrione at 0.27 lb ai/A.[1]

Compound	50 % Mature Foliage		Hay		Hulls		Nutmeat	
	TRR = 0.028 ppm		TRR = 0.012 ppm		TRR = 0.011 ppm		TRR = 0.013 ppm	
	% TRR	ppm	% TRR	ppm	% TRR	ppm	% TRR	ppm
MNBA	12.4	0.003	5.1	0.001	3.6	<0.001	--	--
AMBA	16.7	0.005	6.9	0.001	1.6	<0.001	15.0	0.002
MBA	--	--	3.2	<0.001	--	--	6.7	0.001
4-OH-mesotrione	--	--	--	--	--	--	6.9	0.001
Peak 1	17.6	0.005	13.1	0.002	8.6	0.001	14.0	0.002
Cellulose	10.3	0.003	19.3	0.002	30.1	0.003	15.7	0.002
Lignins	3.1	<0.001	6.3	<0.001	15.5	0.001	0.3	<0.001
Cholesterol ester	--	--	--	--	--	--	12.8	0.002
Triacylglycerols	--	--	--	--	--	--	17.4	0.004
Cholesterol	--	--	--	--	--	--	trace	trace
Diacylglycerols	--	--	--	--	--	--	trace	trace
Monoacylglycerols	--	--	--	--	--	--	7.0	<0001
Fatty acids	--	--	--	--	--	--	4.7	<0.001
Phospholipids	--	--	--	--	--	--	7.0	<0.001
Unknowns - Vials 32-45[2]	1.9	0.001	2.9	<0.001	5.2	0.001	9.9	0.001
Minor unknowns <0.001 ppm[2]	>1.6	<0.001	>1.0	<0.001	>1.4	<0.001	--	--
Acid aqueous (from Blue zone)	0.3	<0.001	0.4	<0.001	--	--	--	--
DCM soluble	7.6	0.002	8.1	0.001	5.0	<0.001	--	--
Chloroform soluble	--	--	--	--	5.3	<0.001	--	--
Aqueous (polysaccharides)	--	--	--	--	8.7	0.001	--	--
ACN/water	--	--	--	--	--	--	3.8	<0.001
Total identified	29.1	0.008	15.2	0.002	5.2	0.001	28.6	0.004
Total characterized	42.4	0.012	51.1	0.006	79.8	0.009	92.6[3]	0.012
Total extractable	94.5	0.026	72.3	0.009	54.2	0.006	132.4[3]	0.017
Unextractable (PES)[4]	13.4	0.004	25.6	0.003	45.6	0.005	16.0	0.002
Accountability[5]	107		100		100		146	

[1] The petitioner did not correct values for loss on further characterization/identification analysis and did not provide quantitative data for unknowns for any fraction except the aqueous fraction following initial partitioning of the ACN/water phase; therefore, the sum of identified and characterized residues does not correspond to the reported total extractable residues.

[2] See Table C.2.2 for distribution of unknowns.

[3] These values are the result of very high recoveries in the aqueous and organic phases following DCM partitioning of the acidified hydrolysate of the nonextractable residues.

[4] Residues remaining after extractions (includes residues characterized as cellulose and lignins following hydrolysis procedures).

[5] Accountability = (Total extractable + Total unextractable)/(TRR from combustion analysis; see TABLE C.2.1) * 100.

TABLE C.2.3.3. Summary of Characterization and Identification of Radioactive Residues in Peanut Matrices Following Application of [Phenyl-U-^{14}C]Mesotrione at 0.71 lb ai/A.[1]

Compound	50 % Mature Foliage		Hay		Hulls		Nutmeat	
	TRR = 0.064 ppm		TRR = 0.028 ppm		TRR = 0.025 ppm		TRR = 0.037 ppm	
	% TRR	ppm	% TRR	ppm	% TRR	ppm	% TRR	ppm
MNBA[2]	11.1	0.007	6.4	0.002	9.6	0.002	2.4	0.001
AMBA	7.1	0.005	4.6	0.001	1.4	<0.001	1.4	0.001
MBA	0.6	<0.001	2.8	<0.001	--	--	--	--
Peak 1	11.2	0.007	32.1	0.009	12.4	0.003	7.0	0.003
Cellulose	23.4	0.015	21.1	0.006	19.6	0.005	43.8	0.016
Lignins	2.2	0.001	2.9	<0.001	0.1	<0.001	6.0	0.002
Cholesterol ester	--	--	--	--	--	--	2.7	0.001
Triacylglycerols	--	--	--	--	--	--	23.5	0.009
Cholesterol	--	--	--	--	--	--	trace	trace
Diacylglycerols	--	--	--	--	--	--	trace	trace
Monoacylglycerols	--	--	--	--	--	--	7.3	0.003
Fatty acids	--	--	--	--	--	--	6.5	0.002
Phospholipids	--	--	--	--	--	--	trace	trace
Unknowns - Vials 32-48/ 42-51/110-116/134-138[3]	2.7	0.002	6.7	0.002	11.4	0.003	--	--
Minor unknowns ~0.001 ppm[3]	>1.3	>0.001	--	--	>1.6	<0.001	--	--
Acid aqueous (from Blue zone)	0.7	<0.001	0.2	<0.001	--	--	--	--
DCM soluble	--	--	6.3	0.002	2.5	<0.001	5.8	0.002
Chloroform soluble	--	--	--	--	2.2	<0.001	--	--
Aqueous (polysaccharides)	5.0	0.003	--	--	5.3	0.001	--	--
ACN/water	--	--	--	--	--	--	3.9	0.001
Total identified	18.8	0.012	13.8	0.004	11.0	0.003	3.8	0.001
Total characterized	46.5	0.030	69.3	0.019	55.1	0.014	106.5	0.039
Total extractable	67.0	0.043	76.3	0.021	57.7	0.014	64.9	0.024
Unextractable (PES)[4]	25.6	0.016	24.0	0.007	19.7	0.005	49.8	0.018
Accountability[5]	92.2		100		76		114	

[1] The petitioner did not correct values for loss on further characterization/identification analysis and did not provide quantitative data for unknowns for any fraction except the aqueous fraction following initial partitioning of the ACN/water phase; therefore, the sum of identified and characterized residues does not correspond to the reported total extractable residues.
[2] Additional MNBA was identified with acid hydrolysis of a separate subsample of the nonextractable residues at 3.2% TRR (0.002 ppm) in 50% mature foliage; 7.1% TRR (0.002 ppm) in hay; 3.5% TRR (0.001 ppm) in hulls; and 2.1% TRR (0.001 ppm) in nutmeats; refer to Table C.2.2.3.
[3] See Table C.2.2 for distribution of unknowns.
[4] Residues remaining after extractions (includes residues characterized as cellulose and lignins following hydrolysis procedures).
[5] Accountability = (Total extractable + Total unextractable)/(TRR from combustion analysis; see TABLE C.2.1) * 100.

C.3. Proposed Metabolic Profile

Based on the submitted CY-label metabolism study, the petitioner proposed that mesotrione is metabolized in peanuts by two pathways. In the first pathway, the cyclohexanedione ring is degraded to CO_2 which is incorporated into natural products, and in the second pathway, the cyclohexanedione ring is oxidized to form 4-hydroxy-mesotrione which is further metabolized to

form multiple metabolites. For PH-labeled mesotrione, metabolism proceeds via cleavage of the cyclohexanedione ring to yield MNBA. MNBA is reduced to its amino analog, AMBA, which is subsequently converted to numerous conjugates or further degraded to MBA. As was observed for the CY label, mesotrione may also undergo hydroxylation to form 4-OH-mesotrione. The petitioner observed that, with the exception of 4-OH-mesotrione, metabolites containing both ring moieties were not characterized in either metabolism study.

FIGURE C.3.1. Proposed Metabolic Profile of CY-Labeled Mesotrione in Peanut

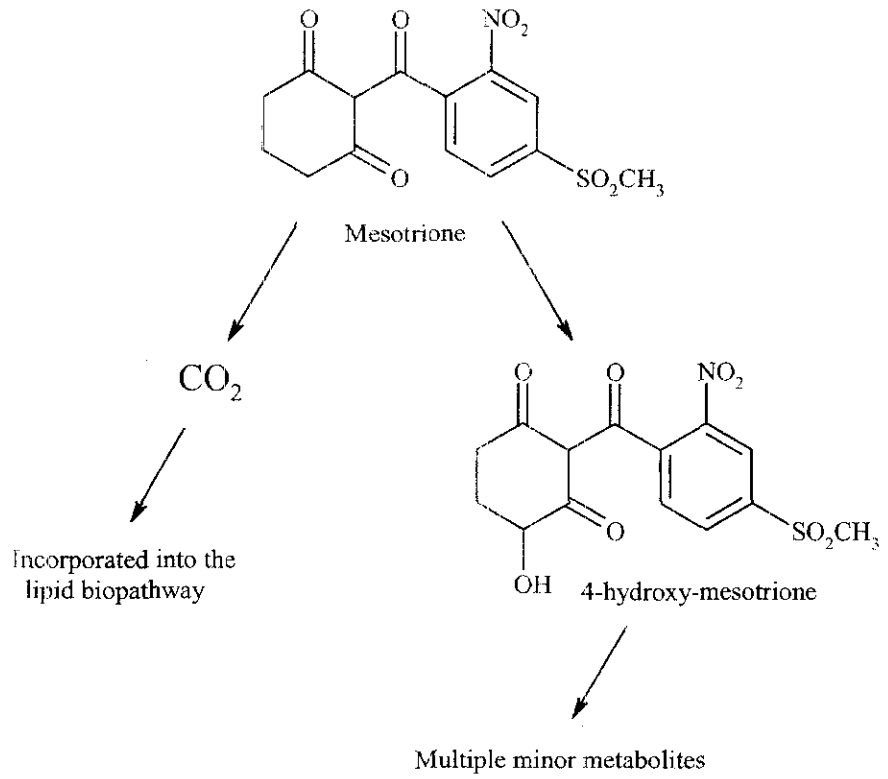


FIGURE C.3.2. Proposed Metabolic Profile of PH-Labeled Mesotrione in Peanut

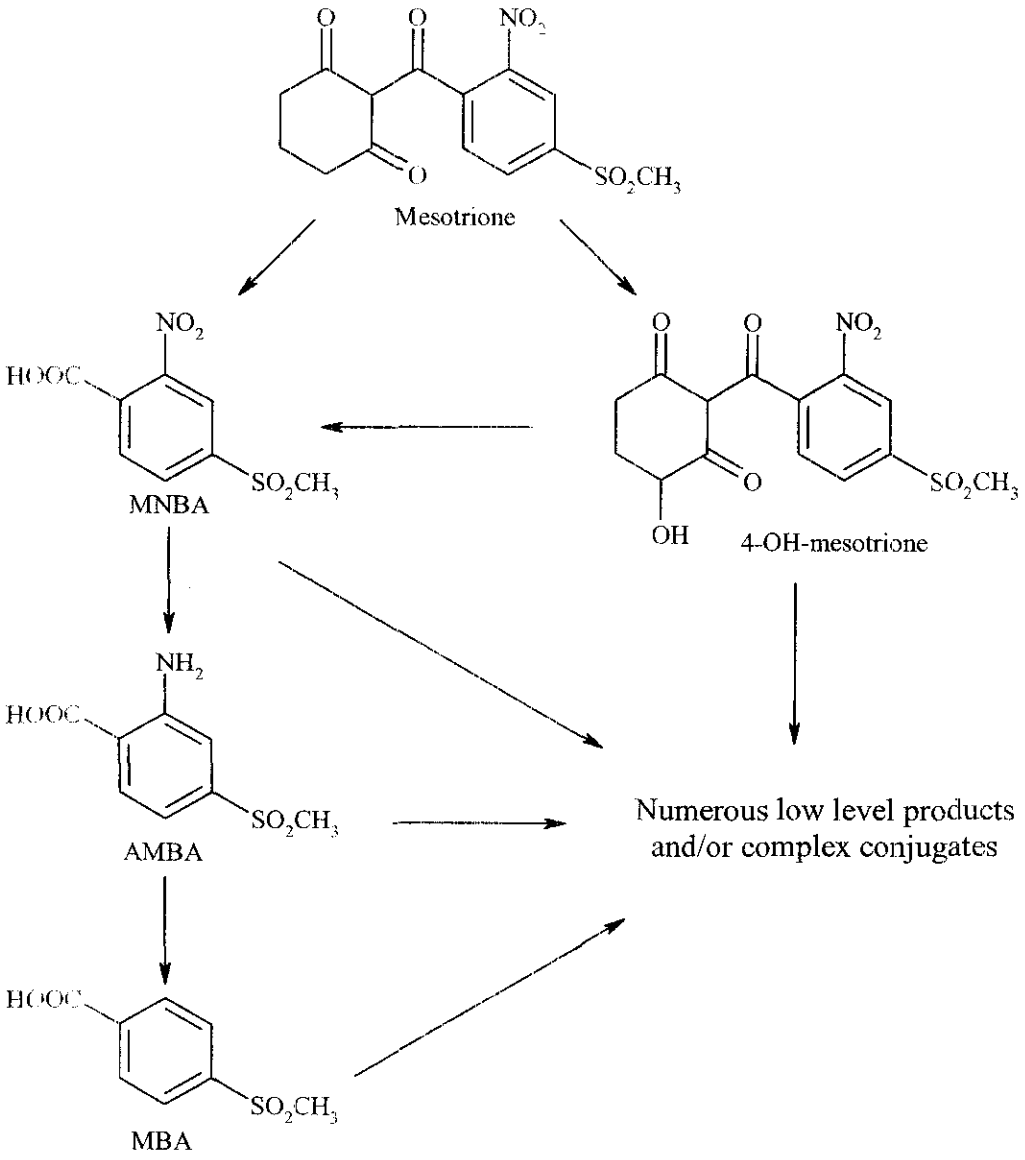
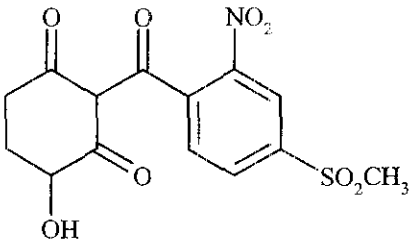
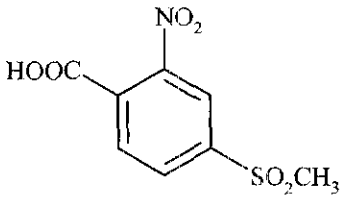
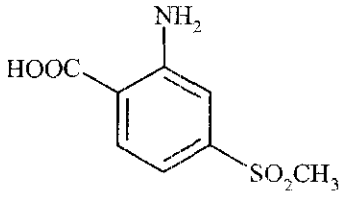
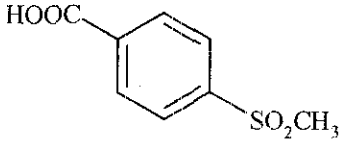


TABLE C.3.1. Identification of Compounds from Metabolism Study.

Common name/code Figure C.3.1 ID No.	Chemical name	Chemical structure
4-hydroxy-mesotrione	4-hydroxy-2-[4-(methylsulfonyl)-2-nitrobenzoyl]-1,3-cyclohexanedione	
MNBA	4-methanesulfonyl-2-nitro-benzoic acid	
AMBA	2-amino-4-methanesulfonyl-benzoic acid	
MBA	4-methanesulfonyl-benzoic acid	

D. CONCLUSION

In separate studies, [cyclohexane-2-^{14}C]mesotrione (CY label) and [phenyl-U-^{14}C]mesotrione (PH label) were applied as a single preemergence application one day after planting peanut seed at nominal rates of 0.29 lb ai/A (327 g ai/ha) and 0.75 lb ai/A (836 g ai/ha) for the CY label, and 0.27 lb ai/A (305 g ai/ha) and 0.71 lb ai/A (796 g ai/ha) for the PH label. Samples of peanut foliage were collected at 50% mature harvest 90 days after application, and samples of mature peanut hay and peanuts were collected 153-154 days after application.

TRR in peanut matrices were determined by combustion/LSC. Following application of CY-labeled mesotrione at 0.29 lb ai/A, TRR were 0.006 ppm in 50% mature foliage, 0.004 ppm in hay, and 0.005 and 0.007 ppm in hulls and nutmeats, respectively. Following application at 0.75 lb ai/A, TRR were 0.020 ppm in foliage, 0.011 ppm in hay, and 0.015 and 0.022 ppm in hulls and nutmeats, respectively. Following application of PH-labeled mesotrione at 0.27 lb ai/A, TRR were 0.028 ppm in 50% mature foliage, 0.012 ppm in hay, and 0.011 and 0.013 ppm in hulls and nutmeats, respectively. Following application at 0.71 lb ai/A, TRR were 0.064 ppm in

foliage, 0.028 ppm in hay, and 0.025 and 0.037 ppm in hulls and nutmeats, respectively. In the CY-label study, only samples from the high rate were subjected to further extraction and analysis for characterization of residues.

In the CY-label study, solvent extraction with ACN/water released ~43%, 27%, and 20% TRR in 50% mature foliage, hay, and hulls respectively. No further attempts were made to release radioactivity from these matrices; nonextractable residues were 65.9-84.5% TRR (0.008-0.013 ppm). Nutmeats were subjected to two separate extraction procedures intended to resolve polar and nonpolar residues. In the first procedure, extraction with ACN/water and ethyl acetate released 43.5% TRR (0.012 ppm); in the second procedure, extraction with hexane and ethyl acetate released 51.4% TRR (0.011 ppm). Nonextractable residues in nutmeat, accounting for ~0.011 ppm, were not further investigated. Because TRR were low in all peanut matrices, HED concludes that the extraction procedures were adequate. Adequate storage stability data were submitted to support the storage intervals and conditions of samples from the study.

In the PH-label study, solvent extraction with ACN/water released ~41-42%, 32-34%, and 20-23% TRR in low- and high-rate 50% mature foliage, hay, and hulls respectively. Additional radioactivity was released from the nonextractable residues by refluxing with water followed by acid and base hydrolysis. These procedures released ~27-52%, 41-42%, and 31-38% TRR in low- and high-rate foliage, hay, and hulls. Remaining nonextractable residues, accounting for 13%, 26%, and 46% TRR in low-rate foliage, hay, and hulls and for 26%, 24%, and 20% TRR in high-rate foliage, hay, and hulls, were characterized as cellulose or lignins on the basis of base and acid hydrolysis. For nutmeats, extraction with hexane released 36% and 32% TRR in low- and high-rate samples, respectively. Additional radioactivity was released from the nonextractable residues by refluxing with water followed by acid and base hydrolysis. These procedures released ~92% TRR in low-rate nutmeats and ~29% TRR in high-rate nutmeats; remaining nonextractable residues, accounting for 16% TRR in low-rate nutmeats and 50% TRR in high-rate nutmeats, were characterized as cellulose or lignin. The extraction procedures for the PH-label study were adequate, and adequate storage stability data were submitted to support the storage intervals and conditions of samples from the study.

Mesotrione was not identified in any peanut matrix following preemergence application of CY-labeled mesotrione. The only identified metabolite was 4-OH-mesotrione, at 1.6% and 1.4% TRR in 50% mature foliage and hay, respectively, and 0.5% TRR in hulls. Minor unknowns (none present at ≥0.001 ppm in any matrix) accounted for 15.1%, 6.0%, and 3.3% TRR in 50% mature foliage, hay, and hulls, and remaining radioactivity was characterized on the basis of anion-exchange chromatography (such as neutral/basic, neutral/acidic, or acidic) and distribution into organic solvents (including ACN, methanol, and ethanol) or aqueous phases. In peanut nutmeats, the distribution of polar residues was similar to that in the other matrices. Nonpolar residues in nutmeats were characterized as neutral lipids, fatty acids, and phospholipids on the basis of elution characteristics on amino SPE. The petitioner confirmed the presence of fatty acids via additional characterization procedures using radiolabeled standards of glycerol and triacylglycerides labeled in the fatty-acid portion of the molecule.

The metabolite profile following preemergence application of PH-labeled mesotrione differed from the profile observed in the CY-label study. Although mesotrione was not identified in any matrix from either treatment rate, metabolites MNBA and AMBA were identified in all matrices, MBA was identified in foliage, hay, and nutmeat, and 4-OH-mesotrione was identified in nutmeat only. MNBA accounted for 12.4%, 5.1%, and 3.6% TRR in low-rate foliage, hay, and hulls, respectively, and was not identified in low-rate nutmeat. In high-rate matrices, MNBA accounted for 11.1%, 6.4%, 9.6%, and 2.4% TRR in high-rate foliage, hay, hulls, and nutmeat, respectively. AMBA was identified in all matrices in the low- and high-rate treatments, at respective levels of 16.7% and 7.1% TRR in foliage, 6.9% and 4.6% TRR in hay, 1.6% and 1.4% TRR in hulls, and 15.0% and 1.4% TRR in nutmeats. MBA was identified at 0.6% TRR in high-rate foliage, 3.2% and 2.8% TRR, respectively, in low- and high-rate hay, respectively, and at 6.7% TRR in low-rate nutmeat. 4-OH-Mesotrione was identified at 6.9% TRR in low-rate nutmeat. Additional residues were characterized as cellulose and lignins on the basis of hydrolysis in all matrices as noted above. Based on extraction from amino SPE columns, residues in low- and high-rate nutmeats, respectively, were characterized as cholesterol esters 12.8% and 2.7% TRR), triacylglycerols (17.4% and 23.5% TRR), and monoacylglycerols (7.0% and 7.3% TRR), fatty acids (4.7% and 6.5% TRR), and phospholipids (7.0% TRR and trace). One major polar unknown, Peak 1 was found in all matrices from low- and high-rate treatments, respectively, at 17.6% and 11.2% TRR in foliage, 13.1% and 32.1% TRR in hay, 8.6% and 12.4% TRR in hulls, and 14.0% and 7.0% TRR in nutmeat. Peak 1 is believed to consist of AMBA conjugates. Discrete unknowns (identified on the basis of fraction collection by vial numbers) accounted for 1.9-11.4% TRR (≤0.003 ppm) in low- and high-rate foliage, hay, and hulls, and low-rate nutmeat, and minor unknowns (none present at ≥0.001 ppm in any matrix) accounted for at least 1.0-1.6% TRR in foliage, hay, and hulls from both rates. Remaining radioactivity was characterized on the basis of distribution into organic solvents (including ACN, methanol, and ethanol) or aqueous phases.

E. REFERENCES

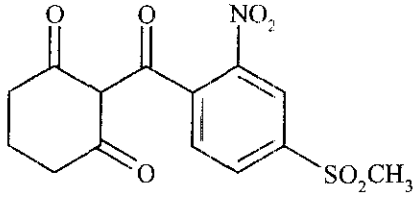
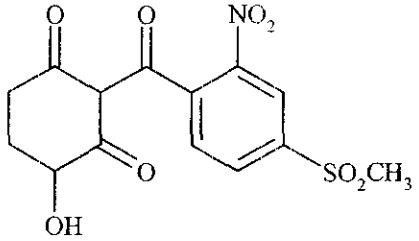
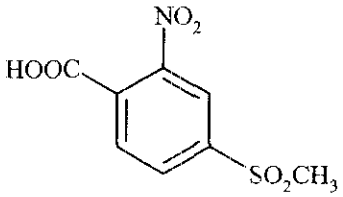
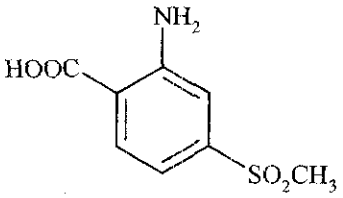
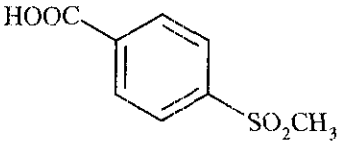
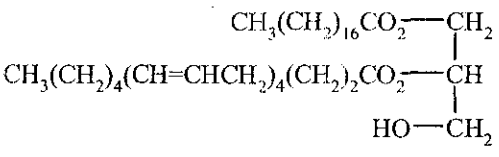
DP#s:	D245477 and D260267
Subject:	PP#: 8F04954. Mesotrione in/on Field Corn. Evaluation of Residue Data and Analytical Methods. PC Code: 122990. Case #: 289589. Submission #s: S541377 and S569871.
From:	S. Levy
To:	J. Stone /J. Tompkins
Date:	06-JUN-2001
MRIDs:	44505118, 44505212-23, 44537109-12, 44901719, and 44942401-03

F. DOCUMENT TRACKING

RDI: G.F. Kramer (02-MAR-2007), RAB1 Chemists (08-NOV-2006)
S. Levy:S10953:PY1:(703)305-0783:7509P:RAB1
Petition#: 6F7023
DP#: 326898
PC Code: 122990

Template Version June 2005

APPENDIX I. Chemical Names and Structures of Reference Standards Used in Peanut Metabolism Studies.

Common name; Company code	Chemical name	Chemical structure
Mesotrione ZA1296	2-[4-(methylsulfonyl)-2-nitrobenzoyl]-1,3-cyclohexanedione	
4-hydroxy-mesotrione [1] R282813	4-hydroxy-2-[4-(methylsulfonyl)-2-nitrobenzoyl]-1,3-cyclohexanedione	
MNBA [1]	4-methanesulfonyl-2-nitro-benzoic acid	
AMBA [1]	2-amino-4-methanesulfonyl-benzoic acid	
MBA	4-methanesulfonyl-benzoic acid	
1-Stearoyl-20-archidonyl-sn-glycerol [1]		
Trimyristin [1]		$[CH_3(CH_2)_{12}CO_2]_3$-C_3H_5
Triolein [1]		$[CH_3(CH_2)_7CH{=}CH(CH_2)_4CO_2]_3$-$C_3H_5$
Tripalmitin [1]		$[CH_3(CH_2)_{14}CO_2]_3$-C_3H_5

APPENDIX I. Chemical Names and Structures of Reference Standards Used in Peanut Metabolism Studies.		
Common name; Company code	Chemical name	Chemical structure
Trilinolenin		$[CH_3(CH_2CH{=}CH)_3(CH_2)_4CO_2]_3\text{-}C_3H_5$

[1] Radiolabeled standard; both radiolabeled and nonlabeled standards of mesotrione, 4-OH-mesotrione, MNBA, and AMBA were used.

Mesotrione/ZA1296/PC Code 122990/ Syngenta Crop Protection, Inc.
DACO 7.4.5/OPPTS 860.1520/OECD IIA 6.5.4 and IIIA 8.5
Processed Food and Feed - Flax

Primary Evaluator: Sarah J. Levy, Chemist
Registration Action Branch (RAB1)
Health Effects Division (HED) (7509P)
Date: 02-MAR-2007

Approved by: George F. Kramer, Ph.D., Senior Chemist
RAB1/HED (7509P)
Date: 02-MAR-2007

This data-evaluation record (DER) was originally prepared under contract by Dynamac Corporation (2275 Research Boulevard, Suite 300; Rockville, MD 20850; submitted 29-SEP-2006). The DER has been reviewed by the HED and revised to reflect current Office of Pesticide Programs (OPP) policies.

STUDY REPORT:

46726303 Lin, K. (2005) Mesotrione: Mesotrione - Magnitude of the Residues in or on Flax and Processed Commodities: Final Report. Project Number: T010290-04. Unpublished study prepared by Syngenta Crop Protection, Inc., Agvise Inc. and Viger Ag Research. 103 p.

EXECUTIVE SUMMARY:

Syngenta Crop Protection has submitted a processing study with mesotrione on flax. In one trial conducted in ND during the 2004 growing season, flax seed was harvested 103 days following a single postemergence, over-the-top broadcast application of the 4 pounds per gallon (lb/gal) flowable-concentrate (FlC) formulation at 0.094, 0.283, or 0.473 lb active ingredient per acre (ai/A). Samples of mature flax seed from the 0.094 lb ai/A and 0.473 lb ai/A treatments, were processed into meal using simulated commercial procedures.

Samples of flax seed and meal were analyzed for residues of mesotrione *per se* using a modified version of a liquid chromatography (LC)/mass spectroscopy (MS)/MS method RAM 366/01. This method was previously reviewed and forwarded to the U.S. Food and Drug Administration (FDA) for inclusion in the Pesticide Analytical Manual (PAM) Volume II as a confirmatory enforcement method for plant commodities (Memo, W. Cutchin, 12-JAN-2005; DP#: 283827). The method is adequate for data collection based on concurrent recovery data. The validated limit of quantitation (LOQ) was 0.01 ppm for mesotrione in/on flax seed and meal.

The maximum storage intervals of crop samples from harvest/processing to analysis were 330 days (10.9 months) for flax seed and 271 days (8.9 months) for processed meal. The petitioner referenced available storage stability data which demonstrate that mesotrione is stable in corn matrices and soybean seed stored frozen for up to 40-42 months (Memo, S. Levy, 06-JUN-2001; DP#: 245477). The available corn and soybean storage stability data will support the storage conditions and intervals of raw agricultural commodity (RAC) samples from the flax seed processing study. There are no data available for meal.

Residues of mesotrione were below the method LOQ (<0.01 ppm) in/on flax seed (RAC) harvested 103 days after a single over-the-top broadcast application with the 4 lb/gal FlC

formulation at 0.094 lb ai/A or 0.473 lb ai/A. Residues of mesotrione were also below the method LOQ (<0.01 ppm) in meal processed from flax seed treated at 0.094 lb ai/A and 0.473 lb ai/A application rates. Processing factors for mesotrione could not be calculated because residues were below the LOQ in/on the RAC and the processed commodity.

STUDY/WAIVER ACCEPTABILITY/DEFICIENCIES/CLARIFICATIONS:

Provided data are submitted validating the meal storage interval, under the conditions and parameters used in the study, the processed commodity residue data are classified as scientifically acceptable. The acceptability of this study for regulatory purposes is addressed in the forthcoming U.S. EPA Residue Chemistry Summary Document [DP#: 326898].

COMPLIANCE:

Signed and dated Good Laboratory Practice (GLP), Quality Assurance and Data Confidentiality statements were provided. No deviations from regulatory requirements were reported which would have an impact on the validity of the study.

A. BACKGROUND INFORMATION

Mesotrione is a triketone herbicide which inhibits the enzyme *p*-hydroxyphenylpyruvate dioxygenase (HPPD), disrupting carotenoid biosynthesis. This process leads to the destruction of chlorophyll, resulting in a bleaching effect in susceptible plants. Mesotrione is intended for preemergence and postemergence use for selective control of annual broadleaf weeds. Mesotrione is currently registered for use on field, pop, and sweet corn.

TABLE A.1. Mesotrione Nomenclature.

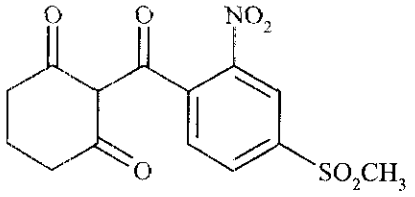
Chemical structure	
Common name	Mesotrione
Company experimental name	ZA1296
IUPAC name	2-(4-mesyl-2-nitrobenzoyl)cyclohexane-1,3-dione
CAS name	2-[4-(methylsulfonyl)-2-nitrobenzoyl]-1,3-cyclohexanedione
CAS registry number	104206-82-8
End-use product (EP)	4 lb/gal FlC (Callisto® Herbicide; EPA Reg. No. 100-1131)

TABLE A.2. Physicochemical Properties of Mesotrione.

Parameter	Value	Reference
Melting range	148.7-152.5°C	RD Memo, H. Podall, 24-FEB-2000; DP#: 263245.
pH	3.4 (1% dispersion in water; 25°C)	
Density	1.46 g/mL, 20°C	

TABLE A.2. Physicochemical Properties of Mesotrione.		
Parameter	Value	Reference
Water solubility	20°C 160 ppm, unbuffered water 0.22 g/100 mL, pH 4.8 1.5 g/100mL, pH 6.9 2.2 g/100 mL, pH 9	
Solvent solubility	20°C 0.37 g/100 mL, methanol 1.7 g/100 mL, ethyl acetate 0.27 g/100 mL, toluene 10.4 g/100 mL, acetonitrile <0.03 g/100 mL, heptane 8.1 g/100 mL, acetone	
Vapor pressure	4.3 x 10^{-8} torr, 20°C	
Dissociation constant, pK_a	3.12, 20°C	
Octanol/water partition coefficient, Log(K_{OW})	20°C log P_{OW} = 0.11 in unbuffered water log P_{OW} = 0.90 in pH 5 buffer log P_{OW} <-1 at pH 7 and 9 buffered water	
UV/visible absorption spectrum	Absorption maximum in methanol at 256 mu, with a molar extinction coefficient of 2.24 x 104 M cm.	

B. EXPERIMENTAL DESIGN

A single trial was conducted in ND during the 2004 growing season. The field test consisted of one untreated plot and three treated plots. Flax seed was harvested 103 days following a single postemergence, over-the-top broadcast application of the 4 lb/gal FlC formulation at 0.094 lb ai/A, 0.283 lb ai/A, or 0.473 lb ai/A. The trial use pattern is reported in Table B.1.1 (refer to the 860.1500 DER for MRID 46726303, for information and study results for the associated flax field trials). Flax seed samples were processed into meal using simulated commercial processing procedures.

B.1. Application and Crop Information

TABLE B.1.1. Study Use Pattern.

Location (County, State; Year) Trial ID	EP[1]	Application						Tank Mix/ Adjuvants
		Method; Timing	Treated Plot	Volume (gal/A)	Rate (lb ai/A)	RTI[2] (days)	Total Rate (lb ai/A)	
Northwood, ND; 2004 (NN-HR-04-5650)	4 lb/gal FlC	Over-the-top broadcast spray; multiple stems and no buds	3	20	0.094	N/A	0.094	None
			4	20	0.283	N/A	0.283	
			5	20	0.473	N/A	0.473	

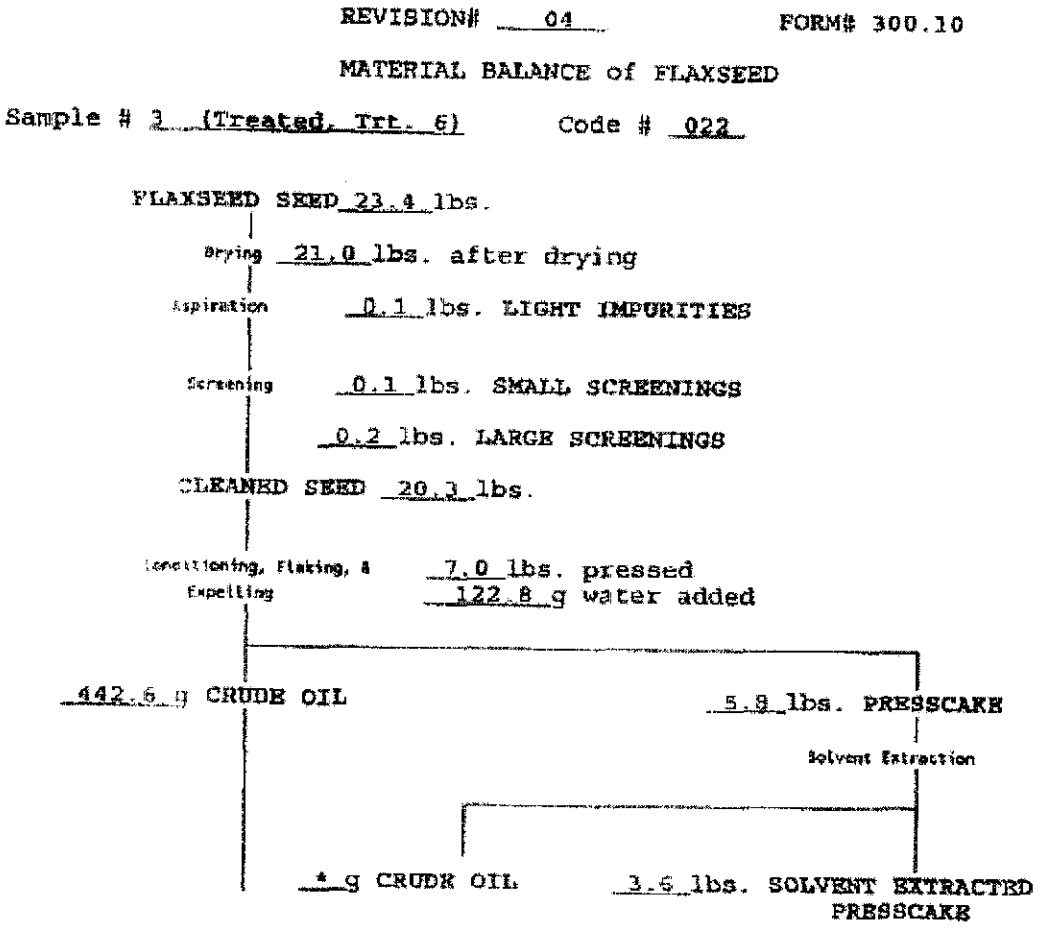
[1] EP = End-use product; Callisto® 4SC Herbicide (EPA Reg. No. 100-1131).
[2] RTI = Retreatment interval; not applicable because a single application was made.

B.2. Sample Handling and Processing Procedures

Bulk untreated and treated flax seed samples (minimum 40 lb each) were collected at maturity; samples from the 0.094 lb ai/A and 0.473 lb ai/A treatments were shipped the next day under ambient conditions to Texas A&M University, Food Protein Research & Development Center (Bryan, TX), where they were stored frozen (~-12°C) until processing. Flax seed was processed within 57-80 days of harvest into expelled crude oil, expelled presscake, and solvent extracted presscake (meal) using simulated commercial processing procedures. The unprocessed RAC and processed meal were stored frozen at Texas A&M, and were shipped frozen to the Syngenta Crop Protection (Greensboro, NC) for residue analysis. Samples were stored frozen (~-15°C) at the analytical laboratory until preparation (ground in the presence of dry ice) and extraction/analysis.

The flax processing procedures are summarized below in Figure 1, which was copied without alteration from the study report.

FIGURE 1. Processing Flowchart for Flax Seed.



* Crude oil from extraction was not weighed. Further refining of oil was not requested.

B.3. Analytical Methodology

Samples of flax seed and meal were analyzed for residues of mesotrione using LC/MS/MS method, RAM 366/01, entitled "Residue Analytical Method for the Determination of Residues of Mesotrione and 4-(Methylsufonyl)-2-Nitrobenzoic Acid (MNBA) in Crop Samples." A detailed description of the method was not included in the study report. This method has been previously reviewed and was forwarded to FDA for inclusion in PAM Vol. II as a confirmatory enforcement method for plant commodities (Memo, W. Cutchin, 12-JAN-2005; DP#: 283827). Minor modifications to the method were made for the analysis of flax matrices (*i.e.*, samples were not analyzed for MNBA (4-methanesulfonyl-2-nitro-benzoic acid), and the solid-phase extraction (SPE) cleanup step was omitted).

Briefly, homogenized samples were mixed with sodium chloride (10:1, wt:wt) and extracted with acetonitrile (ACN):water (1:1, v:v). An aliquot of the extract was diluted with water and the final volume adjusted with 90% water/methanol for LC/MS/MS analysis. The monitored ion transition was m/z 338 → 291. The validated LOQ was 0.01 ppm. The limit of detection (LOD), as determined by the smallest amount of analyte injected, was 0.001 ng for flax matrices.

C. RESULTS AND DISCUSSION

Sample storage conditions and intervals are summarized in Table C.2. Flax seed was processed into meal within 57-80 days of harvest. The maximum storage intervals of crop samples from harvest/processing to analysis were 330 days (10.9 months) for flax seed and 271 days (8.9 months) for processed meal. Actual collection dates for meal samples were not provided; the storage duration is based on the processing completion date. In support of the submitted study, the petitioner referenced available storage stability data which demonstrate that mesotrione was stable in corn matrices and soybean seed stored frozen for up to 40-42 months (Memo, S. Levy, 06-JUN-2001; DP#: 245477). The available corn and soybean storage stability data will support the storage conditions and intervals of RAC samples from the flax seed processing study. Because residues were nonquantifiable in the RAC following treatment at 0.473 lb ai/A, and a processing study would not typically have been required, HED will not require supporting storage stability data for the processed meal samples.

Concurrent recovery data are presented in Table C.1. Samples of flax seed and meal were analyzed for residues of mesotrione *per se* using a modified version of LC/MS/MS method RAM 366/01. This method was previously reviewed and forwarded to FDA for inclusion in PAM Vol. II as a confirmatory enforcement method for plant commodities (refer Memo, W. Cutchin, 12-JAN-2005; DP#: 283827). The method is adequate for data collection based on acceptable concurrent recovery data. The validated LOQ, reflecting the lowest fortifications with acceptable recoveries, was 0.01 ppm for seed and meal. Recoveries were 93% and 85%, respectively, for samples of untreated flax seed and meal fortified at 0.01 ppm. Adequate sample calculations and chromatograms were provided. Apparent residues of mesotrione were below the LOQ in/on two samples each of untreated flax seed and meal.

Residue data from the flax processing study are reported in Table C.3. Residues of mesotrione were below the method LOQ (<0.01 ppm) in/on flax seed (RAC) harvested 103 days after a single postemergence, over-the-top broadcast spray application with the 4 lb/gal FlC formulation at 0.094 lb ai/A or 0.473 lb ai/A. Residues of mesotrione were also below the method LOQ (<0.01 ppm) in meal processed from flax seed treated at 0.094 lb ai/A and 0.473 lb ai/A. Processing factors for mesotrione could not be calculated because residues were below the LOQ in/on the RAC and the processed commodity.

TABLE C.1. Summary of Concurrent Recoveries of Mesotrione from Flax Seed and Meal.				
Matrix	Spike Level (ppm)	Sample Size (n)	Recoveries (%)	Mean ± Std. Dev. (%)
Flax, seed	0.01	1	93	Not applicable (NA)
	1.00	1	104	NA
Flax, meal	0.01	1	85	NA
	1.00	1	102	NA

TABLE C.2. Summary of Storage Conditions.			
Matrix	Storage Temperature (°C)	Actual Storage Duration[1]	Interval of Demonstrated Storage Stability
Flax, seed	~-15	330 days (10.9 months)	Residues of mesotrione are relatively stable in/on fortified soybean seed and corn matrices (forage, stover, and grain) stored frozen for 40-42 months.[2]
Flaxseed, meal	~-15	271 days (8.9 months)	None available.

[1] Interval from harvest/processing to analysis; all samples were analyzed within 1 day of extraction. Seeds were processed within 57-80 days of harvest. Actual collection dates for meal samples were not provided; the storage duration was based on the processing completion date.
[2] Refer to Memo, S. Levy, 06-JUN-2001; DP#: 245477.

TABLE C.3. Residue Data from Flax Processing Study with Mesotrione.					
RAC	Processed Commodity	Total Rate (lb ai/A)	PHI (days)	Residues (ppm)	Processing Factor[1]
Flax seed	seed (RAC)	0.094	103	<0.01	--
	meal			<0.01	NC
	seed (RAC)	0.473	103	<0.01	--
	meal			<0.01	NC

[1] Not calculated (NC) because residues were below the method LOQ (<0.01 ppm) in both the RAC and processed matrix.

D. CONCLUSION

Processing factors for mesotrione in flax could not be calculated because residues were below the method LOQ (<0.01 ppm) in both the RAC and processed meal. An acceptable method was used for quantitation of residues in/on flax seed and meal. Adequate data are available to support sample storage intervals and conditions of the RAC samples; no storage stability data are available for flax meal.

E. REFERENCES

DP#: 263245
Subject: Product Chemistry Review of Mesotrione (ZA 1296 Technical (dry)).
From: H. Podall
To: J. Tompkins/J. Stone
Date: 24-FEB-2000
MRIDs: 44373503-44373505, 44505003, 44505004, and 44901701

DP#s: 245477 and 260267
Subject: PP#: 8F04954. Mesotrione in/on Field Corn. Evaluation of Residue Data and Analytical Methods. PC Code: 122990.
From: S. Levy
To: J. Stone/ J. Tompkins
Dated: 06-JUN-2001
MRIDs: 44505118, 44505212-23, 44537109-12, 44901719, and 44942401-03

DP#: 283827
Subject: Mesotrione. Summary of Analytical Chemistry and Residue Data for Sweet Corn, PP#2F06443, and Response to Data Deficiencies of a Previous HED Review (PP#8F04954, DP Barcodes: D245477 and D260267, 6/6/01, S. Levy).
From: W. Cutchin
To: J. Stone/ J. Miller
Dated: 12-JAN-2005
MRIDs: 45651801-45651803, 45651813, 45651814, 45651816, 45651817, and 45665901

F. DOCUMENT TRACKING

RDI: G.F. Kramer (02-MAR-2007), RAB1 Chemists (15-NOV-2006)
S. Levy:S10953:PY1:(703)305-0783:7509P:RAB1
Petition#: 6F7023
DP#: 326898
PC Code: 122990

Template Version June 2005

Mesotrione/ZA1296/PC Code 122990/ Syngenta Crop Protection, Inc.
DACO 7.4.1/7.4.2/OPPTS 860.1500/OECD IIA 6.3.1, 6.3.2, 6.3.3 and IIIA 8.3.1, 8.3.2, 8.3.3
Crop Field Trial - Flax

Primary Evaluator: Sarah J. Levy, Chemist
Registration Action Branch (RAB1)
Health Effects Division (HED) (7509P)
Date: 02-MAR-2007

Approved by: George F. Kramer, Ph.D., Senior Chemist
RAB1/HED (7509P)
Date: 02-MAR-2007

This data-evaluation record (DER) was originally prepared under contract by Dynamac Corporation (2275 Research Boulevard, Suite 300; Rockville, MD 20850; submitted 29-SEP-2006). The DER has been reviewed by the HED and revised to reflect current Office of Pesticide Programs (OPP) policies.

STUDY REPORT:

46726303 Lin, K. (2005) Mesotrione: Mesotrione - Magnitude of the Residues in or on Flax and Processed Commodities: Final Report. Project Number: T010290-04. Unpublished study prepared by Syngenta Crop Protection, Inc., Agvise Inc. and Viger Ag Research. 103 p.

EXECUTIVE SUMMARY:

Syngenta Crop Protection has submitted field trial data for mesotrione on flax. Five flax trials were conducted in Regions 5 (MN and ND; 2 trials) and 7 (MT, ND, and SD; 3 trials) during the 2004 growing season.

Each field trial site consisted of one untreated plot and three treated plots. Two plots at each site received a single at-planting, broadcast soil application of a 4 pounds per gallon (lb/gal) flowable-concentrate (FlC) formulation of mesotrione at ~0.094 lb active ingredient per acre (ai/A) or ~0.187 lb ai/A. At the third plot, the 4 lb/gal FlC formulation was applied as a single over-the-top broadcast application to flax at the 10" growth stage at ~0.094 lb ai/A. Applications were made using ground equipment in 10-30 gal/A, without an adjuvant. Mature flax seed was harvested 89-170 days after treatment (DAT) from the plots treated at-planting, and 46-130 DAT from the plot treated postemergence. To demonstrate residue decline, additional samples were collected from each treatment plot at the SD trial site 7 days before and after mature harvest.

Samples of flax seed were analyzed for residues of mesotrione *per se* using a modified version of liquid chromatography (LC)/mass spectroscopy (MS)/MS method RAM 366/01. This method was previously reviewed and forwarded to the U.S. Food and Drug Administration (FDA) for inclusion in the Pesticide Analytical Manual (PAM) Volume II as a confirmatory enforcement method for plant commodities (Memo, W. Cutchin, 12-JAN-2005; DP#: 283827). The method is adequate for data collection based on acceptable concurrent recovery data. The validated limit of quantitation (LOQ) was 0.01 ppm for mesotrione in/on flax seed.

The maximum storage interval of flax seed samples from harvest to analysis was 382 days (12.6 months). The petitioner referenced available storage stability data which demonstrate that mesotrione is stable in corn matrices and soybean seed stored frozen for up to 40-42 months

(Memo, S. Levy, 06-JUN-2001; DP#: 245477). The available corn and soybean storage stability data will support the storage conditions and intervals of samples from the subject flax field trials.

Residues of mesotrione were below the method LOQ (<0.01 ppm) in/on all flax seed samples harvested 89-170 days following a single at-planting, soil-surface broadcast application of a 4 lb/gal FlC formulation at 0.093-0.094 lb ai/A or 0.185-0.188 lb ai/A. Residues of mesotrione were also below the method LOQ (<0.01 ppm) in/on all flax seed samples harvested 46-130 days following a single over-the-top broadcast application of the 4 lb/gal FlC formulation at 0.094-0.096 lb ai/A.

Because residues of mesotrione were below the LOQ in/on all flax seed samples from the residue decline study, no conclusions can be made concerning residue decline.

STUDY/WAIVER ACCEPTABILITY/DEFICIENCIES/CLARIFICATIONS:

Under the conditions and parameters used in the study, the field trial residue data are classified as scientifically acceptable. The acceptability of this study for regulatory purposes is addressed in the forthcoming U.S. EPA Residue Chemistry Summary Document [DP#: 326898].

COMPLIANCE:

Signed and dated Good Laboratory Practice (GLP), Quality Assurance and Data Confidentiality statements were provided. No deviations from regulatory requirements were reported which would have an impact on the validity of the study.

A. BACKGROUND INFORMATION

Mesotrione is a triketone herbicide which inhibits the enzyme *p*-hydroxyphenylpyruvate dioxygenase (HPPD), disrupting carotenoid biosynthesis. This process leads to the destruction of chlorophyll, resulting in a bleaching effect in susceptible plants. Mesotrione is intended for preemergence and postemergence use for selective control of annual broadleaf weeds. Mesotrione is currently registered for use on field, pop, and sweet corn.

TABLE A.1. Mesotrione Nomenclature.

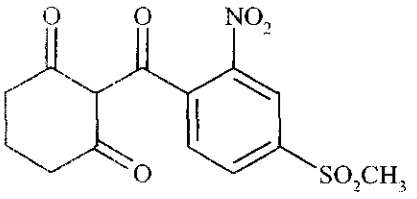
Chemical structure	
Common name	Mesotrione
Company experimental name	ZA1296
IUPAC name	2-(4-mesyl-2-nitrobenzoyl)cyclohexane-1,3-dione
CAS name	2-[4-(methylsulfonyl)-2-nitrobenzoyl]-1,3-cyclohexanedione
CAS registry number	104206-82-8
End-use product (EP)	4 lb/gal FlC (Callisto® Herbicide; EPA Reg. No. 100-1131)

TABLE A.2. Physicochemical Properties of Mesotrione.		
Parameter	Value	Reference
Melting range	148.7-152.5°C	RD Memo, H. Podall, 24-FEB-2000; DP#: 263245.
pH	3.4 (1% dispersion in water; 25°C)	
Density	1.46 g/mL, 20°C	
Water solubility	20°C 160 ppm, unbuffered water 0.22 g/100 mL, pH 4.8 1.5 g/100mL, pH 6.9 2.2 g/100 mL, pH 9	
Solvent solubility	20°C 0.37 g/100 mL, methanol 1.7 g/100 mL, ethyl acetate 0.27 g/100 mL, toluene 10.4 g/100 mL, acetonitrile <0.03 g/100 mL, heptane 8.1 g/100 mL, acetone	
Vapor pressure	4.3 x 10^{-8} torr, 20°C	
Dissociation constant, pK_a	3.12, 20°C	
Octanol/water partition coefficient, Log(K_{ow})	20°C log P_{OW} = 0.11 in unbuffered water log P_{OW} = 0.90 in pH 5 buffer log P_{OW} <-1 at pH 7 and 9 buffered water	
UV/visible absorption spectrum	Absorption maximum in methanol at 256 mu, with a molar extinction coefficient of 2.24 x 104 M cm.	

B. EXPERIMENTAL DESIGN

Five flax trials were conducted in Regions 5 (MN and ND; 2 trials) and 7 (MT, ND, and SD; 3 trials) during the 2004 growing season.

Each field site consisted of one untreated plot and three treated plots. The study use pattern is presented in Table B.1.2. Two plots at each site received a single at-planting, broadcast soil application of a 4 lb/gal FlC formulation of mesotrione at ~0.094 lb ai/A or ~0.187 lb ai/A. At the third plot, the 4 lb/gal FlC formulation was applied as a single over-the-top broadcast application to flax at the 10" growth stage at ~0.094 lb ai/A. Applications were made using ground equipment in 10-30 gal/A, without an adjuvant. Mature flax seed was harvested 89-170 DAT from the plots treated at-planting, and 46-130 DAT from the plot treated postemergence. To demonstrate residue decline, additional samples were collected from each treatment plot at the SD trial site 7 days before and after mature harvest.

Flax was grown under normal agricultural conditions. The petitioner reported cultural practices and maintenance pesticides and fertilizers used at each site. Trial site conditions are presented in Table B.1.1. The crop varieties grown are identified in Table C.3. The petitioner included the overall monthly rainfall and temperature ranges for each trial site and stated that actual temperatures and rainfall amounts were within the average historical ranges at all trial sites. Irrigation was not used at any of the trial sites.

B.1. Study Site Information

TABLE B.1.1. Trial Site Conditions.

Trial Identification: City, State; Year (Trial No.)	Soil characteristics[1]			
	Type	%OM	pH	CEC (meq/g)
Northwood, ND; 2004 (NN-HR-04-5650)	loam	4.4	6.7	23.8
Campbell, MN; 2004 (NF-HR-04-5651)	clay loam	5.5	7.4	33.3
New Rockford, ND; 2004 (NN-HR-04-5652)	sandy loam	2.9	7.2	15.6
Froid, MT; 2004 (NN-HR-04-5653)	loam	2.0	8.1	32.5
Leola, SD; 2004 (NF-HR-04-5654)	loam	6.3	6.8	26.7

[1] OM = organic matter; CEC = cation-exchange capacity.

TABLE B.1.2. Study Use Pattern.

Location: City, State; Year (Trial ID)	EP[1]	Application						Tank Mix/ Adjuvants
		Method; Timing	Treated Plot	Volume (gal/A)	Rate (lb ai/A)	RTI[2] (days)	Total Rate (lb ai/A)	
Northwood, ND; 2004 (NN-HR-04-5650)	4 lb/gal FlC	Broadcast to soil; at planting	1	20	0.094	NA	0.094	None
		Broadcast to soil; at planting	2	20	0.188	NA	0.188	None
		Over-the-top broadcast; multiple stems and no buds	3	20	0.094	NA	0.094	None
Campbell, MN; 2004 (NF-HR-04-5651)	4 lb/gal FlC	Broadcast to soil; at planting	1	30	0.093	NA	0.093	None
		Broadcast to soil; at planting	2	30	0.187	NA	0.187	None
		Over-the-top broadcast; ~10" growth stage	3	20	0.094	NA	0.094	None
New Rockford, ND; 2004 (NN-HR-04-5652)	4 lb/gal FlC	Broadcast to soil; at planting	1	20	0.094	NA	0.094	None
		Broadcast to soil; at planting	2	20	0.187	NA	0.187	None
		Over-the-top broadcast; ~10" growth stage	3	20	0.096	NA	0.096	None
Froid, MT; 2004 (NN-HR-04-5653)	4 lb/gal FlC	Broadcast to soil; at planting	1	10	0.094	NA	0.094	None
		Broadcast to soil; at planting	2	10	0.185	NA	0.185	None
		Over-the-top broadcast; stem elongation	3	10	0.095	NA	0.095	None

TABLE B.1.2. Study Use Pattern.

Location: City, State; Year (Trial ID)	EP[1]	Application						Tank Mix/ Adjuvants
		Method; Timing	Treated Plot	Volume (gal/A)	Rate (lb ai/A)	RTI[2] (days)	Total Rate (lb ai/A)	
Leola, SD; 2004 (NF-HR-04-565)	4 lb/gal FlC	Broadcast to soil; at planting	1	12.5	0.094	NA	0.094	None
		Broadcast to soil; at planting	2	12.5	0.188	NA	0.188	None
		Over-the-top broadcast; ~10" growth stage, BBCH 39	3	12.5	0.094	NA	0.094	None

[1] EP = End-use product; Callisto® 4SC Herbicide (EPA Reg. No. 100-1131).
[2] RTI = Retreatment interval; not applicable (NA) because a single application was made.

TABLE B.1.3. Trial Numbers and Geographical Locations.

NAFTA Growing Regions	Flax		
	Submitted	Requested	
		Canada	U.S.
5	2		2
7	3		3
Total	5		5

B.2. Sample Handling and Preparation

Duplicate control and treated samples of flax seed were harvested from each treatment plot; harvest procedures were not described. All samples were placed in frozen storage at the field sites, and were shipped frozen via ACDS to Syngenta Crop Protection (Greensboro, NC) for residue analysis. Samples were stored frozen (~-15°C) at the analytical laboratory until preparation (ground in the presence of dry ice) and extraction/analysis.

B.3. Analytical Methodology

Samples of flax seed were analyzed for residues of mesotrione using LC/MS/MS method, RAM 366/01, entitled "Residue Analytical Method for the Determination of Residues of Mesotrione and 4-(Methylsufonyl)-2-Nitrobenzoic Acid (MNBA) in Crop Samples." A detailed description of the method was not included in the study report. This method has been previously reviewed and forwarded to FDA for inclusion in PAM Vol. II as a confirmatory enforcement method for plant commodities (Memo, W. Cutchin, 12-JAN-2005; DP#: 283827). Minor modifications to the method were made for the analysis of flax seed (*i.e.*, samples were not analyzed for MNBA (4-methanesulfonyl-2-nitro-benzoic acid), and the solid-phase extraction (SPE) cleanup step was omitted).

Briefly, homogenized samples were mixed with sodium chloride (10:1, wt:wt) and extracted with acetonitrile (ACN):water (1:1, v:v). An aliquot of the extract was diluted with water, and the final volume was adjusted with 90% water/methanol for LC/MS/MS analysis. The monitored ion transition was m/z 338 → 291. The validated LOQ was 0.01 ppm, reflecting the lowest

fortification with acceptable recoveries. The limit of detection (LOD), as determined by the smallest amount of analyte injected, was 0.001 ng for flax seed.

C. RESULTS AND DISCUSSION

Sample storage conditions and intervals are summarized in Table C.2. The maximum storage interval of flax seed samples from harvest to analysis was 382 days (12.6 months). The petitioner referenced available storage stability data which demonstrate that mesotrione was stable in corn matrices and soybean seed stored frozen for up to 40-42 months (Memo, S. Levy, 06-JUN-2001; DP#: 245477). The available corn and soybean storage stability data will support the storage conditions and intervals of samples from the subject flax field trials.

Concurrent recovery data are presented in Table C.1. Samples of flax seed were analyzed for residues of mesotrione *per se* using a modified version of LC/MS/MS method RAM 366/01. This method was previously reviewed and forwarded to FDA for inclusion in PAM Vol. II as a confirmatory enforcement method for plant commodities (Memo, W. Cutchin, 12-JAN-2005; DP#: 283827). The method is adequate for data collection based on acceptable concurrent recovery data. The validated LOQ was 0.01 ppm for mesotrione in/on flax seed. Recoveries ranged 75-113% for samples of untreated flax seed fortified at 0.01 ppm. Adequate sample calculations and chromatograms were provided. Apparent residues of mesotrione were below the LOQ in/on seven untreated samples of flax seed.

Residue data from the flax field trials are reported in Table C.3. A summary of the residue data for flax seed is presented in Table C.4. Residues of mesotrione were below the method LOQ (<0.01 ppm) in/on all flax seed samples harvested 89-170 days following a single at-planting, broadcast soil application of a 4 lb/gal FlC formulation at 0.093-0.094 lb ai/A or 0.185-0.188 lb ai/A. Residues of mesotrione were also below the method LOQ (<0.01 ppm) in/on all flax seed samples harvested 46-130 days following a single over-the-top broadcast application of a 4 lb/gal FlC formulation at 0.094-0.096 lb ai/A.

Because residues of mesotrione were below the LOQ in/on all flax seed samples from the residue decline study, no conclusions can be made concerning residue decline.

TABLE C.1. Summary of Concurrent Recoveries of Mesotrione from Flax Seed.

Matrix	Spike level (ppm)	Sample size (n)	Recoveries (%)	Mean ± std dev (%)
Flax, seed	0.01	6	75, 82, 93, 107, 112, 113	97 ± 16
	1.00	6	87, 87, 95, 100, 104, 113	98 ± 10

TABLE C.2. Summary of Storage Conditions.

Matrix	Storage Temperature (°C)	Actual Storage Duration[1]	Interval of Demonstrated Storage Stability[2]
Flax, seed	~-15	292-382 days (9.6-12.6 months)	Residues of mesotrione are relatively stable in/on fortified soybean seed and corn matrices (forage, stover, and grain) stored frozen for 40-42 months.

[1] Actual storage duration from harvest to analysis. All samples were analyzed within 1-2 days of extraction.
[2] Refer to Memo, S. Levy, 06-JUN-2001; DP#: 245477.

TABLE C.3. Residue Data from Flax Crop Field Trials with Mesotrione.

Trial: City, State, Year (Trial ID)	Region	Crop Variety	Commodity or Matrix	Total Rate (lb ai/A)	PHI (days)	Mesotrione Residues (ppm)
Northwood, ND; 2004 (NN-HR-04-5650)	5	Rehab	seed	0.094 (at planting)	144	<0.01, <0.01
				0.188 (at planting)	144	<0.01, <0.01
				0.094 (postemergence)	103	<0.01, <0.01
Campbell, MN; 2004 (NF-HR-04-5651)	5	York	seed	0.093 (at planting)	170	<0.01, <0.01
				0.187 (at planting)	170	<0.01, <0.01
				0.094 (postemergence)	130	<0.01, <0.01
New Rockford, ND; 2004 (NN-HR-04-5652)	7	Rehab	seed	0.094 (at planting)	136	<0.01, <0.01
				0.187 (at planting)	136	<0.01, <0.01
				0.096 (postemergence)	89	<0.01, <0.01
Froid, MT; 2004 (NN-HR-04-5653)	7	Neche	seed	0.094 (at planting)	89	<0.01, <0.01
				0.185 (at planting)	89	<0.01, <0.01
				0.095 (postemergence)	46	<0.01, <0.01
Leola, SD; 2004 (NF-HR-04-5654)	7	Webster	seed	0.094 (at planting)	133	<0.01, <0.01
					140	<0.01, <0.01
					147	<0.01, <0.01
				0.188 (at planting)	133	<0.01, <0.01
					140	<0.01, <0.01
					147	<0.01, <0.01
				0.094 (postemergence)	95	<0.01, <0.01
					102	<0.01, <0.01
					109	<0.01, <0.01

TABLE C.4. Summary of Residue Data from Crop Field Trials with Mesotrione.

Commodity	Total Applic. Rate (lb ai/A)	PHI (days)	Residue Levels[1] (ppm)						
			n	Min.	Max.	HAFT[2]	Median	Mean	Std. Dev.
At-planting, broadcast to soil									
Flax, seed	0.093-0.094	89-170	10	<0.01	<0.01	<0.01	0.005	0.005	0.0
	0.185-0.188	89-170	10	<0.01	<0.01	<0.01	0.005	0.005	0.0
Over-the-top broadcast									
Flax, seed	0.094-0.096	46-130	10	<0.01	<0.01	<0.01	0.005	0.005	0.0

[1] For calculation of the median, mean, and standard deviation, 0.005 ppm (half the LOQ) was used for residues reported as less than the LOQ in Table C.3.
[2] HAFT = Highest-Average Field Trial.

D. CONCLUSION

Syngenta Crop Protection has submitted data from five field trials for mesotrione on flax during the 2004 growing season. The submitted field trial data reflect the use of a single at-planting, broadcast soil application of a 4 lb/gal FlC formulation at a total rate of 0.093-0.094 lb ai/A or 0.185-0.188 lb ai/A, with a 89- to 170-day PHI for flax seed; OR a single over-the-top broadcast application to flax at the ~10 inch growth stage at 0.094-0.096 lb ai/A, with a 46- to 130-day PHI for seed. Applications were made using ground equipment in 10-30 gal/A, without an adjuvant. Mature flax seed was harvested 89-170 DAT from the plots treated at-planting, and 46-130 DAT from the plot treated postemergence. To demonstrate residue decline, additional samples were collected from each treatment plot at the SD trial site 7 days before and after mature harvest. Residues of mesotrione were below the method LOQ (<0.01 ppm) in/on all flax seed samples. Because residues of mesotrione were below the LOQ in/on all flax seed samples from the residue decline study, no conclusions can be made concerning residue decline. An acceptable method was used for quantitation of residues in/on flax seed, and adequate data are available to support sample storage intervals and conditions.

E. REFERENCES

DP#: 263245
Subject: Product Chemistry Review of Mesotrione (ZA 1296 Technical (dry)).
From: H. Podall
To: J. Tompkins/J. Stone
Date: 24-FEB-2000
MRIDs: 44373503-44373505, 44505003, 44505004, and 44901701

DP#s: 245477 and 260267
Subject: PP#: 8F04954. Mesotrione in/on Field Corn. Evaluation of Residue Data and Analytical Methods. PC Code: 122990.
From: S. Levy
To: J. Stone/ J. Tompkins
Dated: 06-JUN-2001
MRIDs: 44505118, 44505212-23, 44537109-12, 44901719, and 44942401-03

DP#: 283827
Subject: Mesotrione. Summary of Analytical Chemistry and Residue Data for Sweet Corn, PP#2F06443, and Response to Data Deficiencies of a Previous HED Review (PP#8F04954, DP Barcodes: D245477 and D260267, 6/6/01, S. Levy).
From: W. Cutchin
To: J. Stone/ J. Miller
Dated: 12-JAN-2005
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Crop Field Trial - Millet

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Registration Action Branch (RAB1)
Health Effects Division (HED) (7509P)
Date: 02-MAR-2007

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RAB1/HED (7509P)
Date: 02-MAR-2007

This data-evaluation record (DER) was originally prepared under contract by Dynamac Corporation (2275 Research Boulevard, Suite 300; Rockville, MD 20850; submitted 29-SEP-2006). The DER has been reviewed by the HED and revised to reflect current Office of Pesticide Programs (OPP) policies.

STUDY REPORT:

46726302 Lin, K. (2005) Mesotrione: Mesotrione - Magnitude of the Residues in or on Millet: Final Report. Project Number: T010289-04. Unpublished study prepared by Syngenta Crop Protection, Inc., Syngenta Crop Protection, Inc. and Midwest Research, Inc. 124 p.

EXECUTIVE SUMMARY:

Syngenta Crop Protection has submitted field trial data for mesotrione on millet. Five millet trials were conducted in Regions 5 (IL; 1 trial), 7 (NE and SD; 2 trials) and 8 (CO; 2 trials) during the 2004 growing season.

Each field site consisted of one untreated plot and three treated plots. Two plots at each site received a single at-planting, broadcast soil application of a 4 lb/gal flowable-concentrate (FlC) formulation of mesotrione at ~0.094 lb ai/A or ~0.187 lb ai/A. At the third plot, the 4 lb/gal FlC formulation was applied as a single over-the-top broadcast application to millet at the 6" growth stage at ~0.094 lb ai/A. Applications were made using ground equipment in 13-20 gal/A. Spray adjuvants were used for the over-the-top applications at the NE site (nonionic surfactant) and SD site (crop oil concentrate (COC)) only. Immature forage and hay were harvested 31-70 days after treatment (DAT) from plots treated at-planting, and 28-31 DAT from the plots treated postemergence. Mature straw and grain were harvested 84-132 DAT from the plots treated at-planting and 61-113 DAT from the plot treated postemergence. To demonstrate residue decline additional samples were collected from a single trial at ~7 days before and after the target harvest interval from all treatment regimes.

Samples of millet forage, hay, straw, and grain were analyzed for residues of mesotrione *per se* using a modified version of liquid chromatography (LC)/mass spectroscopy (MS)/MS method RAM 366/01. This method was previously reviewed and forwarded to the U.S. Food and Drug Administration (FDA) for inclusion in Pesticide Analytical Manual (PAM) Volume II as a confirmatory enforcement method for plant commodities (Memo, W. Cutchin, 12-JAN-2005; DP#: 283827). The method is adequate for data collection based on acceptable concurrent recovery data. The validated limit of quantitation (LOQ) for this method was 0.01 ppm for mesotrione in/on millet matrices.

The maximum storage interval of millet samples from harvest to analysis was 415 days (13.7 months). The petitioner referenced available storage stability data which demonstrate that mesotrione is stable in corn matrices and soybean seed stored frozen for up to 40-42 months (Memo, S. Levy, 06-JUN-2001; DP#: 245477). The available corn and soybean storage stability data will support the storage conditions and intervals of samples from the subject millet field trials.

Residues of mesotrione were below the method LOQ (<0.01 ppm) following a single at-planting, broadcast soil application of the 4 lb/gal FlC formulation at 0.092-0.098 lb ai/A in/on all samples of millet forage, hay, straw, and grain, except one sample of hay, which bore residues of 0.013 ppm. Maximum residues of mesotrione were 0.014 ppm in/on millet forage and 0.011 ppm in/on hay samples following a single at-planting, broadcast soil application at 0.186-0.194 lb ai/A; residues were below the method LOQ (<0.01 ppm) in/on all millet straw and grain samples following this treatment.

Residues of mesotrione were below the method LOQ (<0.01 ppm) in/on all millet forage, hay, straw, and grain samples following a single over-the-top broadcast application of the 4 lb/gal FlC formulation at 0.092-0.097 lb ai/A.

In the residue decline study, residues of mesotrione were below the LOQ following application at-planting (both rates) in/on all millet forage, hay, straw and grain samples. Following postemergence application, residues of mesotrione were below the LOQ in/on all millet straw and grain samples. Low quantifiable residues were observed at the 23-day pre-harvest interval (PHI) in millet forage (0.010 ppm) and hay (0.013 ppm), but residues declined to below the LOQ by the 30-day target PHI.

STUDY/WAIVER ACCEPTABILITY/DEFICIENCIES/CLARIFICATIONS:

Under the conditions and parameters used in the study, the field trial residue data are classified as scientifically acceptable. The acceptability of this study for regulatory purposes is addressed in the forthcoming U.S. EPA Residue Chemistry Summary Document [DP#: 326898].

COMPLIANCE:

Signed and dated Good Laboratory Practice (GLP), Quality Assurance and Data Confidentiality statements were provided. No deviations from regulatory requirements were reported which would have an impact on the validity of the study.

A. BACKGROUND INFORMATION

Mesotrione is a triketone herbicide which inhibits the enzyme *p*-hydroxyphenylpyruvate dioxygenase (HPPD), disrupting carotenoid biosynthesis. This process leads to the destruction of chlorophyll, resulting in a bleaching effect in susceptible plants. Mesotrione is intended for preemergence and postemergence use for selective control of annual broadleaf weeds. Mesotrione is currently registered for use on field, pop, and sweet corn.

TABLE A.1. Mesotrione Nomenclature.

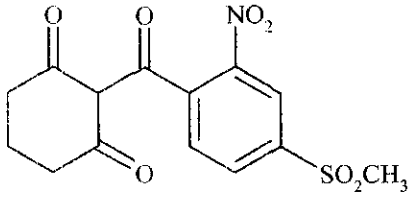
Chemical structure	
Common name	Mesotrione
Company experimental name	ZA1296
IUPAC name	2-(4-mesyl-2-nitrobenzoyl)cyclohexane-1,3-dione
CAS name	2-[4-(methylsulfonyl)-2-nitrobenzoyl]-1,3-cyclohexanedione
CAS registry number	104206-82-8
End-use product (EP)	4 lb/gal FlC (Callisto® Herbicide; EPA Reg. No. 100-1131)

TABLE A.2. Physicochemical Properties of Mesotrione.

Parameter	Value	Reference
Melting range	148.7-152.5°C	RD Memo, H. Podall, 24-FEB-2000; DP# 263245.
pH	3.4 (1% dispersion in water; 25°C)	
Density	*1.46 g/mL, 20°C*	
Water solubility	20°C 160 ppm, unbuffered water 0.22 g/100 mL, pH 4.8 1.5 g/100mL, pH 6.9 2.2 g/100 mL, pH 9	
Solvent solubility	20°C 0.37 g/100 mL, methanol 1.7 g/100 mL, ethyl acetate 0.27 g/100 mL, toluene 10.4 g/100 mL, acetonitrile <0.03 g/100 mL, heptane 8.1 g/100 mL, acetone	
Vapor pressure	4.3×10^{-8} torr, 20°C	
Dissociation constant, pK_a	3.12, 20°C	
Octanol/water partition coefficient, Log(K_{OW})	20°C log P_{OW} = 0.11 in unbuffered water log P_{OW} = 0.90 in pH 5 buffer log P_{OW} <-1 at pH 7 and 9 buffered water	
UV/visible absorption spectrum	Absorption maximum in methanol at 256 mu, with a molar extinction coefficient of 2.24 x 104 M cm.	

B. EXPERIMENTAL DESIGN

Five millet trials were conducted in Regions 5 (IL; 1 trial), 7 (NE and SD; 2 trials) and 8 (CO; 2 trials) during the 2004 growing season.

Each field trial consisted of one untreated plot and three treated plots. The study use pattern is presented in Table B.1.2. Two plots at each site received a single at-planting, broadcast soil application of a 4 lb/gal flowable concentrate (FlC) formulation of mesotrione at ~0.094 lb ai/A or ~0.187 lb ai/A. At the third plot, the 4 lb/gal FlC formulation was applied as a single over-the-top broadcast application to millet at the 6" growth stage at ~0.094 lb ai/A. Applications were made using ground equipment in 13-20 gal/A. Spray adjuvants were used for the over-the-top applications at the NE site (nonionic surfactant) and SD site (COC) only. Immature forage and hay were harvested 31-70 days after treatment (DAT) from plots treated at-planting, and 28-31 DAT from the plots treated postemergence. Mature straw and grain were harvested 84-132 DAT from the plots treated at-planting and 61-113 DAT from the plot treated postemergence. HED notes that no straw samples were collected from the IL site; no explanation was provided by the petitioner. To demonstrate residue decline additional samples were collected from a single trial at ~7 days before and after the target harvest interval from all treatment regimes.

Millet was grown under normal agricultural conditions. The petitioner reported cultural practices and maintenance pesticides and fertilizers used at each site. Trial site conditions are presented in Table B.1.1. The crop varieties grown are identified in Table C.3. The petitioner included the overall monthly rainfall and temperature ranges for each trial site and stated that actual temperatures and rainfall amounts were within the average historical ranges at all trial sites; however, it was noted that smaller samples were collected from the IL trial and one of the CO trials because the crop was drought stressed. Irrigation was used to supplement rainfall at the IL and NE trial sites and one CO trial site.

B.1. Study Site Information

TABLE B.1.1. Trial Site Conditions.

Trial Identification: City, State; Year (Trial No.)	Soil characteristics[1]			
	Type	%OM	pH	CEC (meq/g)
Champaign, IL; 2004 (4A-HR-04-5640)	silty clay loam	2.0	7	0.21
Grand Island, NE; 2004 (NB-HR-04-5641)	silt loam	2.9	6.4	0.23
Ideal, SD; 2004 (NF-HR-04-5642)	clay loam	3.2	6.6	0.277
Ault, CO; 2004 (NM-HR-04-5643)	sandy clay loam	2.0	8.1	0.223
Ault, CO; 2004 (NM-HR-04-5644)	sandy clay loam	1.4	8.3	0.276

[1] OM = organic matter; CEC = cation-exchange capacity.

TABLE B.1.2. Study Use Pattern.

Location: City, State; Year (Trial ID)	EP[1]	Application						Tank Mix/ Adjuvants
		Method; Timing	Treated Plot	Volume (gal/A)	Rate (lb ai/A) [g ai/A]	RTI[2] (days)	Total Rate (lb ai/A)	
Champaign, IL; 2004 (4A-HR-04-5640)	4 lb/gal FlC	Broadcast to soil; at planting	1	16	0.097	NA	0.097	None
		Broadcast to soil; at planting	2	16	0.191	NA	0.191	None
		Over-the-top broadcast; ~6" growth stage, BBCH 32	3	13	0.097	NA	0.097	None
Grand Island, NE; 2004 (NB-HR-04-5641)	4 lb/gal FlC	Broadcast to soil; at planting	1	20	0.092	NA	0.092	None
		Broadcast to soil; at planting	2	20	0.187	NA	0.187	None
		Over-the-top broadcast; ~6" growth stage, BBCH 12	3	20	0.092	NA	0.092	NIS (0.25%, v/v)
Ideal, SD; 2004 (NF-HR-04-5642)	4 lb/gal FlC	Broadcast to soil; at planting	1	19	0.093	NA	0.093	None
		Broadcast to soil; at planting	2	19	0.186	NA	0.186	None
		Over-the-top broadcast; ~6" growth stage, BBCH 21	3	20	0.093	NA	0.093	COC (1% v/v)
Ault, CO; 2004 (NM-HR-04-5643)	4 lb/gal FlC	Broadcast to soil; at planting	1	16	0.096	NA	0.096	None
		Broadcast to soil; at planting	2	16	0.189	NA	0.189	None
		Over-the-top broadcast; ~6" growth stage, vegetative	3	14	0.096	NA	0.096	None
Ault, CO; 2004 (NM-HR-04-5644)	4 lb/gal FlC	Broadcast to soil; at planting	1	16	0.098	NA	0.098	None
		Broadcast to soil; at planting	2	16	0.194	NA	0.194	None
		Over-the-top broadcast; ~6" growth stage, vegetative	3	14	0.096	NA	0.096	None

[1] EP = End-use product; Callisto® 4SC Herbicide (EPA Reg. No. 100-1131).
[2] RTI = Retreatment interval; not applicable (NA) because a single application was made.

TABLE B.1.3. Trial Numbers and Geographical Locations.

NAFTA Growing Regions	Millet		
	Submitted	Requested	
		Canada	U.S.
1			
5	1		1
7	2		2
8	2		2
Total	5		5

HED notes that the two CO trials were conducted at the same field site using the same variety of millet, and that the crops were treated on the same date by the same field director. HED has examined the field records for these trials and concludes that they represent separate trials because, based on soil characteristics and irrigation records, the trials were conducted at different fields, and the crops reached maturity on different dates.

B.2. Sample Handling and Preparation

Duplicate control and treated samples of millet immature forage and hay, and mature straw and grain were harvested from each treatment plot (~3 lbs each of forage and grain, and ~2 lbs each of hay and straw); harvest procedures were not described. Smaller samples were collected from the IL trial and one of the CO trials because the crop was drought stressed. Hay samples were dried in the field for 1-5 days, except at the CO trials where hay samples were air-dried for 30 hours prior to sampling. HED notes that the IL trial reported that the grain samples from the postemergence treated plot were dried for 24 days prior to sampling. All samples were placed in frozen storage at the field sites, and were shipped frozen via ACDS truck or overnight by FedEx to Syngenta Crop Protection (Greensboro, NC) for residue analysis. Samples were stored frozen (~-15°C) at the analytical laboratory until preparation for extraction/analysis. Samples of forage, hay, and straw were prepared by cutting into 2" pieces and grinding in the presence of dry ice. Grain was prepared by removing chaff and/or other debris by blowing, sifting, or by hand, and milling in the presence of dry ice.

B.3. Analytical Methodology

Samples of millet commodities were analyzed for residues of mesotrione using LC/MS/MS method, RAM 366/01, entitled "Residue Analytical Method for the Determination of Residues of Mesotrione and 4-(Methylsufonyl)-2-Nitrobenzoic Acid (MNBA) in Crop Samples." A detailed description of the method was not included in the study report. This method has been previously reviewed and forwarded to FDA for inclusion in PAM Vol. II as a confirmatory enforcement method for plant commodities (Memo, W. Cutchin, 12-JAN-2005; DP#: 283827). Minor modifications were made to the method for the analysis of millet matrices (*i.e.*, samples were not analyzed for MNBA (4-methanesulfonyl-2-nitro-benzoic acid), and the solid-phase extraction (SPE) cleanup step was omitted).

Briefly, homogenized samples were mixed with sodium chloride (10:1, wt:wt) and extracted with acetonitrile (ACN):water (1:1, v:v). An aliquot of the extract was diluted with water and the final volume adjusted with 90% water/methanol for LC/MS/MS analysis. The monitored ion transition was m/z 338 → 291. The validated LOQ was 0.01 ppm. The limit of detection (LOD), as determined by the smallest amount of analyte injected, was 0.001 ng for millet commodities.

C. RESULTS AND DISCUSSION

Sample storage conditions and intervals are summarized in Table C.2. The maximum storage interval of millet samples from harvest to analysis was 415 days (13.7 months). The petitioner referenced available storage stability data which demonstrate that mesotrione is stable in corn matrices and soybean seed stored frozen for up to 40-42 months (Memo, S. Levy, 06-JUN-2001; DP#: 245477). The available corn and soybean storage stability data will support the storage conditions and intervals of samples from the subject millet field trials.

Samples of millet forage, hay, straw, and grain were analyzed for residues of mesotrione *per se* using a modified version of LC/MS/MS method RAM 366/01. This method was previously reviewed and forwarded to FDA for inclusion in PAM Vol. II as a confirmatory enforcement method for plant commodities (Memo, W. Cutchin, 12-JAN-2005; DP#: 283827). The method is adequate for data collection based on acceptable concurrent recovery data. The validated LOQ was 0.01 ppm. Recoveries ranged 71-114% for samples of untreated millet forage, hay, straw, and grain fortified with mesotrione at 0.01 ppm. Adequate sample calculations and chromatograms were provided. Apparent residues of mesotrione were below the LOQ in/on seven untreated samples each of millet forage, hay, straw, and grain.

Residue data from the millet field trials are reported in Table C.3. A summary of the residue data for millet forage, hay, straw, and grain is presented in Table C.4.

Residues of mesotrione were below the method LOQ (<0.01 ppm) following a single at-planting, broadcast soil application of the 4 lb/gal FlC formulation at 0.092-0.098 lb ai/A in/on all samples of millet forage, hay, straw, and grain, except one sample of hay, which bore residues of 0.013 ppm. Maximum residues of mesotrione were 0.014 ppm in/on millet forage and 0.011 ppm in/on hay samples following a single at-planting, broadcast soil application at 0.186-0.194 lb ai/A; residues were below the method LOQ (<0.01 ppm) in/on all millet straw and grain samples following this treatment.

Residues of mesotrione were below the method LOQ (<0.01 ppm) in/on all millet forage, hay, straw, and grain samples following a single over-the-top broadcast application of the 4 lb/gal FlC formulation at 0.092-0.097 lb ai/A.

In the residue decline study, residues of mesotrione were below the LOQ following application at-planting (both rates) in/on all millet forage, hay, straw and grain samples. Following postemergence application, residues of mesotrione were below the LOQ in/on all millet straw and grain samples. Low quantifiable residues were observed at the 23-day PHI in millet forage

(0.010 ppm) and hay (0.013 ppm), but residues declined to below the LOQ by the 30-day PHI (target PHI).

TABLE C.1. Summary of Concurrent Recoveries of Mesotrione from Millet Matrices.

Matrix	Spike level (ppm)	Sample size (n)	Recoveries (%)	Mean ± std dev (%)
Millet, forage	0.01	7	71, 73, 77, 79, 87, 87, 92	81 ± 8
	1.00	7	85, 86, 87, 90, 93, 95, 102	91 ± 6
Millet, hay	0.01	7	71, 72, 73, 73, 77, 83, 100	78 ± 10
	1.00	7	77, 79, 84, 84, 85, 92, 98	86 ± 7
Millet, straw	0.01	6	75, 77, 83, 108, 111, 114	95 ± 18
	1.00	5	84, 84, 88, 95, 112	93 ± 12
Millet, grain	0.01	7	75, 76, 80, 81, 84, 108, 113	88 ± 16
	1.00	6	77, 84, 88, 90, 98, 103	90 ± 9

TABLE C.2. Summary of Storage Conditions.

Matrix	Storage Temperature (°C)	Actual Storage Duration[1]	Interval of Demonstrated Storage Stability[2]
Millet, forage	~-15	300-414 days (9.9-13.6 months)	Residues of mesotrione are relatively stable in/on fortified soybean seed and corn matrices (forage, stover, and grain) stored frozen for 40-42 months.
Millet, hay		338-415 days (11.1-13.7 months)	
Millet, straw		297-351 days (9.8-11.5 months)	
Millet, grain		297-352 days (9.8-11.6 months)	

[1] Duration from harvest to analysis. All samples were analyzed within 1-16 days of extraction.
[2] Memo, S. Levy, 06-JUN-2001; DP#: 245477.

TABLE C.3. Residue Data from Crop Field Trials with Mesotrione.

Trial: City, State: Year (Trial ID)	Region	Crop; Variety	Commodity or Matrix	Application Timing	Total Rate (lb ai/A)	PHI[1] (days)	Mesotrione Residues (ppm)
Champaign, IL; 2004 (4A-HR-04-5640)	5	Millet; Pearl Max	forage	At planting	0.097	31	<0.01, <0.01
					0.191	31	<0.01, <0.01
				Postemergence	0.097	31	<0.01, <0.01
			hay	At planting	0.097	31 (3)	<0.01, <0.01
					0.191	31 (3)	<0.01, <0.01
				Postemergence	0.097	31	<0.01, <0.01
			grain	At planting	0.097	130	<0.01, <0.01
					0.192	130	<0.01, <0.01
				Postemergence	0.097	113 (24)	<0.01, <0.01
Grand Island, NE; 2004 (NB-HR-04-5641)	7	Millet; Huntsman	forage	At planting	0.092	51	<0.01, <0.01
					0.187	51	<0.01, <0.01
				Postemergence	0.092	28	<0.01, <0.01
			hay	At planting	0.092	51 (4)	<0.01, <0.01
					0.187	51 (4)	<0.01, <0.01
				Postemergence	0.092	28 (4)	<0.01, <0.01
			straw	At planting	0.092	84	<0.01, <0.01
					0.187	84	<0.01, <0.01
				Postemergence	0.092	61	<0.01, <0.01
			grain	At planting	0.093	84	<0.01, <0.01
					0.187	84	<0.01, <0.01
				Postemergence	0.093	61	<0.01, <0.01
Ideal, SD; 2004 (NF-HR-04-5642)	7	Millet; Rise	forage	At planting	0.093	34	<0.01, <0.01
					0.186	34	<0.01, 0.014
				Postemergence	0.093	30	<0.01, <0.01
			hay	At planting	0.093	34 (5)	<0.01, 0.013
					0.186	34 (5)	0.011, 0.011
				Postemergence	0.093	30 (4)	<0.01, <0.01
			straw	At planting	0.093	95	<0.01, <0.01
					0.186	95	<0.01, <0.01
				Postemergence	0.093	69	<0.01, <0.01
			grain	At planting	0.093	95	<0.01, <0.01
					0.186	95	<0.01, <0.01
				Postemergence	0.093	69	<0.01, <0.01

TABLE C.3. Residue Data from Crop Field Trials with Mesotrione.

Trial: City, State: Year (Trial ID)	Region	Crop; Variety	Commodity or Matrix	Application Timing	Total Rate (lb ai/A)	PHI[1] (days)	Mesotrione Residues (ppm)
Ault, CO; 2004 (NM-HR-04-5643)	8	Millet; Early Bird	forage	At planting	0.096	70	<0.01, <0.01
					0.189	70	<0.01, <0.01
				Postemergence	0.096	30	<0.01, <0.01
			hay	At planting	0.096	70 (1.25)	<0.01, <0.01
					0.189	70 (1.25)	<0.01, <0.01
				Postemergence	0.096	30 (1.25)	<0.01, <0.01
			straw	At planting	0.096	132	<0.01, <0.01
					0.189	132	<0.01, <0.01
				Postemergence	0.096	92	<0.01, <0.01
			grain	At planting	0.096	132	<0.01, <0.01
					0.189	132	<0.01, <0.01
				Postemergence	0.096	92	<0.01, <0.01
Ault, CO; 2004 (NM-HR-04-5644)	8	Millet; Early Bird	forage	At planting	0.098	63	<0.01, <0.01
						70*	<0.01, <0.01
						77	<0.01, <0.01
					0.194	63	<0.01, <0.01
						70*	<0.01, <0.01
						77	<0.01, <0.01
				Postemergence	0.096	23	<0.01, 0.01
						30*	<0.01, <0.01
						37	<0.01, <0.01
			hay	At planting	0.098	63 (2)	<0.01, <0.01
						70 (2)*	<0.01, <0.01
						77 (2)	<0.01, <0.01
					0.194	63 (2	<0.01, <0.01
						70 (2)*	<0.01, <0.01
						77 (2)	<0.01, <0.01
				Postemergence	0.096	23 (2)	0.013, 0.013
						30 (2)*	<0.01, <0.01
						37 (2)	<0.01, <0.01
			straw	At planting	0.098	104	<0.01, <0.01
						111*	<0.01, <0.01
						120	<0.01, <0.01
					0.194	104	<0.01, <0.01
						111*	<0.01, <0.01
						120	<0.01, <0.01
				Postemergence	0.096	64	<0.01, <0.01
						71*	<0.01, <0.01
						80	<0.01, <0.01

TABLE C.3. Residue Data from Crop Field Trials with Mesotrione.

Trial: City, State; Year (Trial ID)	Region	Crop; Variety	Commodity or Matrix	Application Timing	Total Rate (lb ai/A)	PHI[1] (days)	Mesotrione Residues (ppm)
Ault, CO; 2004 (NM-HR-04-5644) -continued			grain	At planting	0.098	104	<0.01, <0.01
						111*	<0.01, <0.01
						120	<0.01, <0.01
					0.194	104	<0.01, <0.01
						111*	<0.01, <0.01
						120	<0.01, <0.01
				Postemergence	0.096	64	<0.01, <0.01
						71*	<0.01, <0.01
						80	<0.01, <0.01

[1] Days dried prior to sampling are reported in parentheses. Mature harvest for residue decline is marked by an asterisk.

TABLE C.4. Summary of Residue Data from Crop Field Trials with Mesotrione.

Commodity	Total Applic. Rate (lb ai/A)	PHI (days)	Residue Levels[1] (ppm)						
			n	Min.	Max.	HAFT[2]	Median	Mean	Std. Dev.
At-planting, soil surface									
Millet, forage	0.092-0.098	31-70	10	<0.01	<0.01	<0.01	0.005	0.005	0.0
Millet, hay		31-70	10	<0.01	0.013	<0.01	0.005	0.006	0.002
Millet, straw		84-132	10	<0.01	<0.01	<0.01	0.005	0.005	0.0
Millet grain		84-132	10	<0.01	<0.01	<0.01	0.005	0.005	0.0
Millet, forage	0.186-0.194	31-70	10	<0.01	0.014	<0.012	0.005	0.006	0.003
Millet, hay		31-70	10	<0.01	0.011	0.011	0.005	0.006	0.003
Millet, straw		84-132	10	<0.01	<0.01	<0.01	0.005	0.005	0.0
Millet grain		84-132	10	<0.01	<0.01	<0.01	0.005	0.005	0.0
Postemergence, over-the-top									
Millet, forage	0.092-0.097	28-31	10	<0.01	<0.01	<0.01	0.005	0.005	0.0
Millet, hay		28-31	10	<0.01	<0.01	<0.01	0.005	0.005	0.0
Millet, straw		61-113	10	<0.01	<0.01	<0.01	0.005	0.005	0.0
Millet grain		61-113	10	<0.01	<0.01	<0.01	0.005	0.005	0.0

[1] For calculation of the median, mean, and standard deviation, 0.005 ppm (half the LOQ) was used for residues reported as less than the LOQ in Table C.3.
[2] HAFT = Highest-Average Field Trial.

D. CONCLUSION

Syngenta Crop Protection has submitted field trial data for mesotrione on millet. Five millet field trials were conducted during the 2004 growing season. The submitted field trial data reflect a single at-planting, broadcast soil application of a 4 lb/gal FlC formulation at a total rate of 0.093-0.097 lb ai/A or 0.185-0.194 lb ai/A, with a 31- to 70-day PHI for forage and hay, and an 84- to 132-day PHI for straw and grain; OR a single over-the-top broadcast application at 0.093-0.097 lb ai/A to millet at the ~6-inch growth stage, with a 28- to 31-day PHI for forage and hay, and a 61- to 113-day PHI for straw and grain. An acceptable method was used for quantitation

of residues in/on millet commodities, and adequate data are available to support sample storage intervals and conditions.

Residues of mesotrione were below the method LOQ (<0.01 ppm) following a single at-planting, broadcast soil application of the 4 lb/gal FlC formulation at 0.092-0.098 lb ai/A in/on all samples of millet forage, hay, straw, and grain, except one sample of hay, which bore residues of 0.013 ppm. Maximum residues of mesotrione were 0.014 ppm in/on millet forage and 0.011 ppm in/on hay samples following a single at-planting, broadcast soil application at 0.186-0.194 lb ai/A; residues were below the method LOQ (<0.01 ppm) in/on all millet straw and grain samples following this treatment.

Residues of mesotrione were below the method LOQ (<0.01 ppm) in/on all millet forage, hay, straw, and grain samples following a single over-the-top broadcast application of the 4 lb/gal FlC formulation at 0.092-0.097 lb ai/A.

In the residue decline study, residues of mesotrione were below the LOQ following application at-planting (both rates) in/on all millet forage, hay, straw and grain samples. Following postemergence application, residues of mesotrione were below the LOQ in/on all millet straw and grain samples. Low quantifiable residues were observed at the 23-day pre-harvest interval (PHI) in millet forage (0.010 ppm) and hay (0.013 ppm), but residues declined to below the LOQ by the 30-day target PHI.

E. REFERENCES

DP#:	263245
Subject:	Product Chemistry Review of Mesotrione (ZA 1296 Technical (dry)).
From:	H. Podall
To:	J. Tompkins/J. Stone
Date:	24-FEB-2000
MRIDs:	44373503-44373505, 44505003, 44505004, and 44901701
DP#s:	245477 and 260267
Subject:	PP#: 8F04954. Mesotrione in/on Field Corn. Evaluation of Residue Data and Analytical Methods. PC Code: 122990.
From:	S. Levy
To:	J. Stone/ J. Tompkins
Dated:	06-JUN-2001
MRID(s):	44505118, 44505212-23, 44537109-12, 44901719, and 44942401-03
DP#:	283827
Subject:	Mesotrione. Summary of Analytical Chemistry and Residue Data for Sweet Corn, PP#2F06443, and Response to Data Deficiencies of a Previous HED Review (PP#8F04954, DP Barcodes: D245477 and D260267, 6/6/01, S. Levy).
From:	W. Cutchin
To:	J. Stone/ J. Miller
Dated:	12-JAN-2005
MRID(s):	45651801-45651803, 45651813, 45651814, 45651816, 45651817, and 45665901

F. DOCUMENT TRACKING

RD1: G.F. Kramer (02-MAR-2007), RAB1 Chemists (15-NOV-2006)
S. Levy:S10953:PY1:(703)305-0783:7509P:RAB1
Petition#: 6F7023
DP#: 326898
PC Code: 122990

Template Version June 2005

Mesotrione/ZA1296/PC Code 122990/ Syngenta Crop Protection, Inc.
DACO 7.4.1/7.4.2/OPPTS 860.1500/OECD IIA 6.3.1, 6.3.2, 6.3.3 and IIIA 8.3.1, 8.3.2, 8.3.3
Crop Field Trial - Berry Group 13

Primary Evaluator: Sarah J. Levy, Chemist
Registration Action Branch (RAB1)
Health Effects Division (HED) (7509P)
Date: 02-MAR-2007

Approved by: George F. Kramer, Ph.D., Senior Chemist
RAB1/HED (7509P)
Date: 02-MAR-2007

This data-evaluation record (DER) was originally prepared under contract by Dynamac Corporation (2275 Research Boulevard, Suite 300; Rockville, MD 20850; submitted 29-SEP-2006). The DER has been reviewed by the HED and revised to reflect current Office of Pesticide Programs (OPP) policies.

STUDY REPORT:

46726301 Lin, K. (2005) Mesotrione: Mesotrione - Magnitude of the Residues in or on Berry, Group 13: Final Report. Project Number: T010288-04. Unpublished study prepared by Syngenta Crop Protection, Inc., A.C.D.S. Research, Inc. and Agricultural Systems Associates. 92 p.

EXECUTIVE SUMMARY:

Syngenta Crop Protection has submitted field trial data for mesotrione on the representative crops of the berry group, crop group 13. A total of ten berry trials were conducted during the 2004-2005 growing season. Six blueberry trials were conducted in Regions 1 (NY; 1 trial), 2 (NC; 2 trials), 5 (MI; 2 trials), and 12 (WA; 1 trial); three raspberry trials were conducted in Regions 5 (MI; 1 trial) and 12 (OR; 2 trials); and one blackberry trial was conducted in Region 12 (OR).

At each trial location, a single pre-bloom directed spray application of a 4 pounds per gallon (lb/gal) flowable-concentrate (FlC) formulation of mesotrione was made at ~0.094 lb active ingredient per acre (ai/A) or ~0.187 lb ai/A. Applications were made using ground equipment in spray volumes of 24-62 gal/A, without an adjuvant. Berries were harvested at maturity, 34-88 days after application. Additional samples were collected from one blueberry and one raspberry trial 7 and 4 days prior to and 4 days after mature harvest (pre-harvest intervals (PHIs) of 32, 35, and 49 days and 67, 70, and 78 days, respectively).

Samples of blueberries, raspberries, and blackberries were analyzed for residues of mesotrione *per se* using a modified version of liquid chromatography (LC)/mass spectroscopy (MS)/MS method RAM 366/01. This method was previously reviewed and forwarded to the U.S. Food and Drug Administration (FDA) for inclusion in the Pesticide Analytical Manual (PAM) Volume II as a confirmatory enforcement method for plant commodities (Memo, W. Cutchin, 12-JAN-2005; DP#: 283827). The method is adequate for data collection based on acceptable concurrent recovery data. The validated limit of quantitation (LOQ) was 0.01 ppm for mesotrione in/on berries.

The maximum storage interval of berry samples from harvest to analysis was 501 days (16.4 months). No storage stability data are available and none were submitted to support the storage intervals and conditions of samples from the berry field trials; however, the petitioner stated that the results of a storage stability study demonstrating the stability of mesotrione residues in/on berries stored frozen for 17 months will be submitted to the Agency upon completion.

Residues of mesotrione were below the method LOQ (<0.01 ppm) in/on all blueberry, raspberry, and blackberry samples harvested 34-88 days following a prebloom, directed spray treatment with the 4 lb/gal FlC formulation at 0.091-0.098 lb ai/A or 0.185-0.195 lb ai/A.

Because residues of mesotrione were below the LOQ in/on all blueberry and raspberry samples from the residue decline studies, no conclusions can be made concerning residue decline.

STUDY/WAIVER ACCEPTABILITY/DEFICIENCIES/CLARIFICATIONS:

Under the conditions and parameters used in the study, the field trial residue data are tentatively classified as scientifically acceptable pending submission of the results of the storage stability study for residues of mesotrione in berries stored frozen for up to 17 months.

The acceptability of this study for regulatory purposes is addressed in the forthcoming U.S. EPA Residue Chemistry Summary Document [DP#: 326898].

COMPLIANCE:

Signed and dated Good Laboratory Practice (GLP), Quality Assurance and Data Confidentiality statements were provided. No deviations from regulatory requirements were reported which would have an impact on the validity of the study.

A. BACKGROUND INFORMATION

Mesotrione is a triketone herbicide which inhibits the enzyme *p*-hydroxyphenylpyruvate dioxygenase (HPPD), disrupting carotenoid biosynthesis. This process leads to the destruction of chlorophyll, resulting in a bleaching effect in susceptible plants. Mesotrione is intended for preemergence and postemergence use for selective control of annual broadleaf weeds. Mesotrione is currently registered for use on field, pop, and sweet corn.

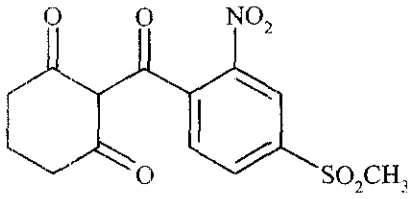
TABLE A.1. Mesotrione Nomenclature.	
Chemical structure	
Common name	Mesotrione
Company experimental name	ZA1296
IUPAC name	2-(4-mesyl-2-nitrobenzoyl)cyclohexane-1,3-dione
CAS name	2-[4-(methylsulfonyl)-2-nitrobenzoyl]-1,3-cyclohexanedione
CAS registry number	104206-82-8
End-use product (EP)	4 lb/gal FIC (Callisto® Herbicide; EPA Reg. No. 100-1131)

TABLE A.2. Physicochemical Properties of Mesotrione.		
Parameter	Value	Reference
Melting range	148.7-152.5°C	RD Memo, H. Podall, 24-FEB-2000; DP#: 263245.
pH	3.4 (1% dispersion in water; 25°C)	
Density	1.46 g/mL, 20°C	
Water solubility	20°C 160 ppm, unbuffered water 0.22 g/100 mL, pH 4.8 1.5 g/100mL, pH 6.9 2.2 g/100 mL, pH 9	
Solvent solubility	20°C 0.37 g/100 mL, methanol 1.7 g/100 mL, ethyl acetate 0.27 g/100 mL, toluene 10.4 g/100 mL, acetonitrile <0.03 g/100 mL, heptane 8.1 g/100 mL, acetone	
Vapor pressure	4.3 x 10^{-8} torr, 20°C	
Dissociation constant, pK_a	3.12, 20°C	
Octanol/water partition coefficient, Log(K_{OW})	20°C log P_{OW} = 0.11 in unbuffered water log P_{OW} = 0.90 in pH 5 buffer log P_{OW} <-1 at pH 7 and 9 buffered water	
UV/visible absorption spectrum	Absorption maximum in methanol at 256 mu, with a molar extinction coefficient of 2.24 x 104 M cm.	

B. EXPERIMENTAL DESIGN

A total of ten trials were conducted on the representative crops of the berry group, crop group 13 during the 2004-2005 growing season. Six blueberry trials were conducted in Regions 1 (NY; 1 trial), 2 (NC; 2 trials), 5 (MI; 2 trials), and 12 (WA; 1 trial); three raspberry trials were conducted in Regions 5 (MI; 1 trial) and 12 (OR; 2 trials); and one blackberry trial was conducted in Region 12 (OR).

Each field trial consisted of one untreated plot and two treated plots. The study use pattern is presented in Table B.1.2. At each trial, a single pre-bloom directed spray application of a 4 lb/gal FlC formulation of mesotrione was made at ~0.094 lb ai/A or ~0.187 lb ai/A (42.5 g ai/A or 85 g ai/A, respectively). Applications were made using ground equipment (backpack or tractor-mounted sprayer) in spray volumes of 24-62 gal/A, without an adjuvant. HED notes that applications to blueberries at the NC sites were actually made at early fruit set, and applications at the WA site were made with fruit present, plants still blooming.

Berries were grown under normal agricultural conditions. Trial site conditions are presented in Table B.1.1. The crop varieties grown are identified in Table C.3. The petitioner included the overall monthly rainfall and temperature ranges for each trial site and stated that actual temperatures and rainfall amounts were within the average historical ranges at all trial sites. Irrigation was used to supplement rainfall at the WA (blueberry) and OR (raspberry) trial sites.

B.1. Study Site Information

TABLE B.1.1. Trial Site Conditions.

Trial Identification: City, State; Year (Trial No.)	Soil characteristics[1]			
	Type	%OM	pH	CEC (meq/g)
Blueberry				
Penn Yan, NY; 2004 (5A-HR-04-5630)	gravelly loam	3.3	4.9	8.6
Rose Hill, NC; 2004 (SJ-HR-04-5631)	sand	4.3	3.7	7.0
Rose Hill, NC; 2004 (SJ-HR-04-5632)	sand	1.6	4.0	4.6
Fremont, MI; 2004 (NL-HR-04-5633)	loamy sand	3.2	4.5	5.3
Conklin, MI; 2004 (NL-HR-04-5634)	loam	2.1	4.5	12.8
LaConner, WA; 2004 (WF-HR-04-5635)	silt loam	5.9	5.0	23.3
Raspberry				
Belding, MI; 2004 (NL-HR-04-5636)	loam	1.7	4.7	9.3
Corvallis, OR; 2004 (WG-HR-04-5637)	silty clay loam	2.4	6.5	17.4
Corvallis, OR; 2005 (WG-HR-05-6370)	silty clay loam	2.4	6.5	17.4
Blackberry				
Hillsboro, OR; 2004 (WG-HR-04-5638)	loam	4.9	5.3	16.6

[1] OM = organic matter; CEC = cation-exchange capacity.

TABLE B.1.2. Study Use Pattern.

Location: City, State; Year (Trial ID)	EP[1]	Application						Tank Mix/ Adjuvants
		Method; Timing	Treated Plot	Volume (gal/A)	Rate (lb ai/A)	RTI[2] (days)	Total Rate (lb ai/A)	
Blueberry								
Penn Yan, NY, 2004 (5A-HR-04-5630)	4 lb/gal FlC	Directed pre-bloom; crop growth stage 59	1	50	0.091	N/A	0.091	None
			2	49	0.188	N/A	0.188	None
Rose Hill, NC, 2004 (SJ-HR-04-5631)	4 lb/gal FlC	Directed pre-bloom; early fruit set	1	27	0.096	N/A	0.096	None
			2	28	0.193	N/A	0.193	None
Rose Hill, NC, 2004 (SJ-HR-04-5632)	4 lb/gal FlC	Directed pre-bloom; early fruit set	1	28	0.098	N/A	0.098	None
			2	27	0.190	N/A	0.190	None
Fremont, MI; 2004 (NL-HR-04-5633)	4 lb/gal FlC	Directed pre-bloom; early pink bud	1	53	0.094	N/A	0.094	None
			2	52	0.186	N/A	0.186	None
Conklin, MI; 2004 (NL-HR-04-5634)	4 lb/gal FlC	Directed pre-bloom; pink bud	1	52	0.094	N/A	0.094	None
			2	53	0.189	N/A	0.189	None
LaConner, WA; 2004 (WF-HR-04-5635)	4 lb/gal FlC	Directed pre-bloom; fruit present, plants still blooming	1	30	0.092	N/A	0.092	None
			2	30	0.187	N/A	0.187	None
Raspberry								
Belding, MI; 2004 (NL-HR-04-5636)	4 lb/gal FlC	Directed pre-bloom; pre-bloom, 2-3 leaves present	1	53	0.094	N/A	0.094	None
			2	52	0.185	N/A	0.185	None
Corvallis, OR; 2004 (WG-HR-04-5637)	4 lb/gal FlC	Directed pre-bloom; crop growth stage 51	1	25	0.094	N/A	0.094	None
			2	25	0.186	N/A	0.186	None
Corvallis, OR; 2005 (WG-HR-05-6370)	4 lb/gal FlC	Directed pre-bloom; crop growth stage 51	1	61	0.097	N/A	0.097	None
			2	62	0.189	N/A	0.189	None
Blackberry								
Hillsboro, OR; 2004 (WG-HR-04-5638)	4 lb/gal FlC	Directed pre-bloom; pre-bloom	1	24	0.096	N/A	0.096	None
			2	24	0.195	N/A	0.195	None

[1] EP = End-use product; Callisto® 4SC Herbicide (EPA Reg. No. 100-1131).
[2] RTI = Retreatment Interval; not applicable (N/A) because a single application was made.

TABLE B.1.3. Trial Numbers and Geographical Locations.

NAFTA Growing Regions	Berry, Crop Group 13					
	Blueberry			Blackberry/Raspberry		
	Submitted	Requested		Submitted	Requested	
		Canada	U.S.		Canada	U.S.
1	1		1			
2	2		2			
5	2		2	1 (raspberry)		
12	1		1	2 (raspberry) 1 (blackberry)		
Total	6		6[1]	4		3[2]

[1] As required by OPPTS 860.1500, Tables 2 and 5, for blueberries and blackberries or raspberries as representative members of the berry group, crop group 13. The number of trials for blueberries reflects a 25% reduction; because only three trials are required for blackberries or raspberries, no reduction is permitted.

[2] Geographic distribution of field trials for blackberries/raspberries is not specified because the number of trials is ≤3; however, *Table 5 identifies Regions* 2, 5 (raspberry), 6 (blackberry), and 12 for suggested distribution of field trials for individual tolerances.

HED notes that the NC blueberry trials were conducted on the same variety of blueberries, and were treated on the same date at the same location by the same field director. HED has examined the field records for these trials and concludes that they represent separate trials because the plants were treated with different spray mixtures and berries reached maturity on different dates.

B.2. Sample Handling and Preparation

Duplicate control and treated samples (~3 lbs each) of mature blueberries, raspberries, or blackberries were harvested (method not specified) at maturity, 34-88 days after application. Additional samples (~0.5 lb each) were collected from one blueberry and one raspberry trial 7 and 4 days prior to and 4 days after mature harvest (PHIs of 32, 35, and 49 days and 67, 70, and 78 days, respectively) to demonstrate residue decline. All samples were placed in frozen storage at the field sites, and were shipped frozen to Syngenta Crop Science (Greensboro, NC) for residue analysis. Samples were stored frozen (~-15°C) at the analytical laboratory until preparation (caps and stems removed, homogenization in the presence of dry ice) and extraction/analysis.

B.3. Analytical Methodology

Samples of blueberries, raspberries, and blackberries were analyzed for residues of mesotrione using LC/MS/MS method, RAM 366/01, entitled "Residue Analytical Method for the Determination of Residues of Mesotrione and 4-(Methylsufonyl)-2-Nitrobenzoic Acid (MNBA) in Crop Samples." A detailed description of the method was not included in the study report. This method has been previously reviewed and was forwarded to FDA for inclusion in PAM Vol. II as a confirmatory enforcement method for plant commodities (Memo, W. Cutchin, 12-JAN-2005; DP#: 283827). Minor modifications to the method were made for the analysis of berries (*i.e.*, samples were not analyzed for MNBA (4-methanesulfonyl-2-nitro-benzoic acid), and the solid-phase extraction (SPE) cleanup step was omitted for some samples).

Briefly, homogenized samples were mixed with sodium chloride (10:1, wt:wt) and extracted with acetonitrile (ACN):water (1:1, v:v). An aliquot of the extract was diluted with formic acid, and cleaned up by SPE on a polymeric column; residues were eluted with methanol:formic acid (98:2, v:v). The eluate was evaporated to dryness, and residues were redissolved in 90% water/methanol for LC/MS/MS analysis. For some samples, the cleanup step was omitted; instead, an aliquot of the ACN/water extract was diluted with water, and the final volume was adjusted with water/methanol for analysis. The monitored ion transition was m/z 338 → 291. The validated LOQ was 0.01 ppm, reflecting the lowest fortification with acceptable recoveries. The limit of detection (LOD), as determined by the smallest amount of analyte injected, was 0.001 ng.

C. RESULTS AND DISCUSSION

Sample storage conditions and intervals are summarized in Table C.2. The maximum storage interval of berry samples from harvest to analysis was 501 days (16.4 months). No storage stability data were submitted to support the storage intervals and conditions of samples from the berry field trials; however, the petitioner stated that the results of a storage stability study demonstrating the stability of mesotrione residues in/on berries stored frozen for 17 months will be submitted to the Agency upon completion. The petitioner also referenced available storage stability data which demonstrate that mesotrione is stable in other crops (corn matrices, radish root, and soybean seed) stored frozen for up to 40-44 months (Memo, S. Levy, 06-JUN-2001; DP#: 245477); however, these data cannot be translated to berries because the data do not reflect a fruit or fruiting vegetable.

Concurrent recovery data are presented in Table C.1. Samples of berries were analyzed for residues of mesotrione *per se* using a modified version of LC/MS/MS method RAM 366/01. This method was previously reviewed and forwarded to FDA for inclusion in PAM Vol. II as a confirmatory enforcement method for plant commodities (Memo, W. Cutchin, 12-JAN-2005; DP#: 283827). The method is adequate for data collection based on concurrent recovery data. The validated LOQ was 0.01 ppm for mesotrione in/on berries. Recoveries ranged 75-102% for samples of blueberries, blackberries, and raspberries fortified at 0.01 ppm. Adequate sample calculations and chromatograms were provided. Apparent residues of mesotrione were below the LOQ in/on all samples of untreated blueberry, raspberry, and blackberry samples.

Residue data from the berry field trials are reported in Table C.3. A summary of the residue data for blueberry, raspberry, and blackberry is presented in Table C.4. Residues of mesotrione were below the method LOQ (<0.01 ppm) in/on all blueberry, raspberry, and blackberry samples harvested 34-88 days following single post-emergence, pre-bloom, directed spray application of a 4 lb/gal FlC formulation at total seasonal rates of 0.091-0.098 lb ai/A or 0.185-0.195 lb ai/A.

Because residues of mesotrione were below the LOQ in/on all blueberry and raspberry samples from the residue decline studies, no conclusions can be made concerning residue decline.

TABLE C.1. Summary of Concurrent Recoveries of Mesotrione from Blueberry, Raspberry and Blackberry.

Matrix	Spike level (ppm)	Sample size (n)	Recoveries (%)	Mean ± std dev (%)
Blueberry	0.01	9	77, 78, 81, 82, 83, 84, 88, 91, 95	84 ± 6
	1.00	5	67, 94, 97, 102, 104	93 ± 15
Raspberry	0.01	6	75, 85, 89, 92, 97, 102	90 ± 9
	1.00	3	84, 98, 101	94 ± 9
Blackberry	0.01	1	87	Not applicable

TABLE C.2. Summary of Storage Conditions.

Matrix	Storage Temperature (°C)	Actual Storage Duration[1]	Interval of Demonstrated Storage Stability
Berries	~-15	95-501 days (3.1-16.4 months)	None available

[1] Interval from harvest to analysis. All samples were analyzed within 7 days of extraction.

TABLE C.3. Residue Data from Crop Field Trials with Mesotrione.

Trial: City, State; Year (Trial ID)	Region	Crop; Variety	Commodity or Matrix	Total Rate (lb ai/A)	PHI (days)	Mesotrione Residues (ppm)
Penn Yan, NY; 2004 (5A-HR-04-5630)	1	Blueberry; Blue Ray	berry	0.091	77	<0.01, <0.01
				0.188	77	<0.01, <0.01
Rose Hill, NC; 2004 (SJ-HR-04-5631)	2	Blueberry; Reveille	berry	0.096	32	<0.01, <0.01
					35	<0.01, <0.01
					39	<0.01, <0.01
					43	<0.01, <0.01
				0.193	32	<0.01, <0.01
					35	<0.01, <0.01
					39	<0.01, <0.01
					43	<0.01, <0.01
Rose Hill, NC; 2004 (SJ-HR-04-5632)	2	Blueberry; Reveille	berry	0.098	34	<0.01, <0.01
				0.190	34	<0.01, <0.01
Fremont, MI; 2004 (NL-HR-04-5633)	5	Blueberry; Blue Crop	berry	0.094	72	<0.01, <0.01
				0.186	72	<0.01, <0.01
Conklin, MI; 2004 (NL-HR-04-5634)	5	Blueberry; Blue Ray	berry	0.094	64	<0.01, <0.01
				0.189	64	<0.01, <0.01
LaConner, WA; 2004	12	Blueberry;	berry	0.092	88	<0.01, <0.01

TABLE C.3. Residue Data from Crop Field Trials with Mesotrione.

Trial: City, State; Year (Trial ID)	Region	Crop; Variety	Commodity or Matrix	Total Rate (lb ai/A)	PHI (days)	Mesotrione Residues (ppm)
(WF-HR-04-5635)		Nelson & Elliots		0.187	88	<0.01, <0.01
Belding, MI; 2004 (NL-HR-04-5636)	5	Raspberry; K81-6	berry	0.094	67	<0.01, <0.01
					70	<0.01, <0.01
					74	<0.01, <0.01
					78	<0.01, <0.01
				0.185	67	<0.01, <0.01
					70	<0.01, <0.01
					74	<0.01, <0.01
					78	<0.01, <0.01
Corvallis, OR; 2004 (WG-HR-04-5637)	12	Raspberry; Caroline	berry	0.094	52	<0.01, <0.01
				0.186	52	<0.01, <0.01
Corvallis, OR; 2005 (WG-HR-05-6370)	12	Raspberry; Caroline	berry	0.097	83	<0.01, <0.01
				0.189	83	<0.01, <0.01
Hillsboro, OR; 2004 (WG-HR-04-5638)	12	Blackberry; Kotata	berry	0.096	62	<0.01, <0.01
				0.195	62	<0.01, <0.01

TABLE C.4. Summary of Residue Data from Crop Field Trials with Mesotrione.

Commodity	Total Applic. Rate (lb ai/A)	PHI (days)	Residue Levels[1] (ppm)						
			n	Min.	Max.	HAFT[2]	Median	Mean	Std. Dev.
Blueberry	0.091-0.098	32-88	12	<0.01	<0.01	<0.01	0.005	0.005	0.0
	0.186-0.193	32-88	12	<0.01	<0.01	<0.01	0.005	0.005	0.0
Raspberry	0.094-0.097	52-83	6	<0.01	<0.01	<0.01	0.005	0.005	0.0
	0.185-0.189	52-83	6	<0.01	<0.01	<0.01	0.005	0.005	0.0
Blackberry	0.096	62	2	<0.01	<0.01	<0.01	0.005	0.005	0.0
	0.195	62	2	<0.01	<0.01	<0.01	0.005	0.005	0.0

[1] For calculation of the median, mean, and standard deviation 0.005 ppm (half the LOQ) was used for residues reported below the LOQ in Table C.3.
[2] HAFT = Highest-Average Field Trial.

D. CONCLUSION

Syngenta Crop Protection has submitted field trial data for mesotrione on the representative crops of the berry group, crop group 13. A total of ten berry trials were conducted during the 2004-2005 growing season (six blueberry trials; three raspberry trials; and one blackberry trial).

At each trial location, a single pre-bloom directed spray application of a 4 lb/gal FlC mesotrione formulation was made at 0.091-0.098 lb ai/A or 0.185-0.195 lb ai/A. Applications were made using ground equipment in spray volumes of 24-62 gal/A, without an adjuvant. Berries were harvested at maturity, 34-88 days after application. Additional samples were collected from one blueberry and one raspberry trial 7 and 4 days prior to and 4 days after mature harvest (PHIs of 32, 35, and 49 days and 67, 70, and 78 days, respectively).

Residues of mesotrione were below the method LOQ (<0.01 ppm) in/on all blueberry, raspberry, and blackberry samples at 0.091-0.098 lb ai/A or 0.185-0.195 lb ai/A. An acceptable method was used for quantitation of residues in/on cranberries, but data are not available to support sample storage intervals and conditions.

E. REFERENCES

DP#: 263245
Subject: Product Chemistry Review of Mesotrione (ZA 1296 Technical (dry)).
From: H. Podall
To: J. Tompkins/J. Stone
Date: 24-FEB-2000
MRIDs: 44373503-44373505, 44505003, 44505004, and 44901701

DP#s: 245477 and 260267
Subject: PP#: 8F04954. *Mesotrione in/on* Field Corn. Evaluation of Residue Data and Analytical Methods. PC Code: 122990.
From: S. Levy
To: J. Stone/ J. Tompkins
Dated: 06-JUN-2001
MRIDs: 44505118, 44505212-23, 44537109-12, 44901719, and 44942401-03

DP#: 283827
Subject: Mesotrione. Summary of Analytical Chemistry and Residue Data for Sweet Corn, PP#2F06443, and Response to Data Deficiencies of a Previous HED Review (PP#8F04954, DP Barcodes: D245477 and D260267, 6/6/01, S. Levy).
From: W. Cutchin
To: J. Stone/ J. Miller
Dated: 12-JAN-2005
MRIDs: 45651801-45651803, 45651813, 45651814, 45651816, 45651817, and 45665901

F. DOCUMENT TRACKING

RDI: G.F. Kramer (02-MAR-2007), RAB1 Chemists (15-NOV-2006)
S. Levy:S10953:PY1:(703)305-0783:7509P:RAB1
Petition #: 6F7023
DP#: 326898
PC Code: 122990

Template Version June 2005

Primary Evaluator: Sarah J. Levy, Chemist
Registration Action Branch (RAB1)
Health Effects Division (HED) (7509P)

Date: 02-MAR-2007

Approved by: George F. Kramer, Ph.D., Senior Chemist
RAB1/HED (7509P)

Date: 02-MAR-2007

This data-evaluation record (DER) was originally prepared under contract by Dynamac Corporation (2275 Research Boulevard, Suite 300; Rockville, MD 20850; submitted 09/29/2006). The DER has been reviewed by the HED and revised to reflect current Office of Pesticide Programs (OPP) policies.

STUDY REPORT:

46726306 Ray, W. (2005) [Phenyl-U-^{14}C) Mesotrione: Nature of the Residue in Cranberries: Final Report. Project Number: T014117-04. Unpublished study prepared by Syngenta Crop Protection, Inc. 70 p.

EXECUTIVE SUMMARY:

Syngenta Crop Protection, Inc. has submitted a study investigating the metabolism of [phenyl-U-^{14}C]mesotrione (PH label; specific activity 40.8 µCi/mg for low-rate applications and 21.1 µCi/mg for high-rate applications) in cranberries. The radiolabeled test substances were formulated as emulsifiable concentration (EC) formulations and applied as two broadcast foliar applications to cranberries 33 and 49 days post-transplant at 0.30 and 0.22 lb ai/A for a total application rate of 0.52 lb ai/A (low rate), or 0.82 and 0.57 lb ai/A for a total application rate of 1.39 lb ai/A (high rate). Samples of cranberries and foliage were collected at maturity, 46 days after the last application.

Total radioactive residues (TRR) were 2.573 ppm in cranberries and 16.832 ppm in foliage collected 46 days following the low-rate application, and 4.853 ppm in cranberries and 31.804 ppm in foliage collected 46 days following the high-rate application. Only cranberries were subjected to analysis for residue characterization and identification.

Solvent extraction with acetonitrile (ACN)/water released a reported ~103% TRR in low-rate cranberries and ~102% TRR in high-rate cranberries. Nonextractable residues accounted for 2.5% TRR (0.064 ppm) in low-rate cranberries and 2.2% TRR (0.107 ppm) in high-rate cranberries. Accountabilities were 104-105%. The extraction procedures were adequate. Residues were identified and quantitated by high-performance liquid chromatography (HPLC), and identification of metabolites was confirmed by thin-layer chromatography (TLC) co-chromatography and by liquid chromatography (LC)/mass spectrometry (MS)/MS (mesotrione only). Adequate storage stability data were submitted to support the storage intervals and conditions of samples from the study.

Mesotrione was the major residue identified in cranberries, accounting for 60.2% TRR (1.548 ppm) in low-rate cranberries and for 67.1% TRR (3.257 ppm) in high-rate cranberries. The metabolite AMBA (2-amino-4-methanesulfonyl-benzoic acid), identified after peak isolation and acid hydrolysis, was also a significant component, accounting for 34.8% TRR (0.895 ppm) in low-rate cranberries and for 24.3% TRR (1.178 ppm) in high rate cranberries. Metabolite MNBA (4-methanesulfonyl-2-nitro-benzoic acid) was identified at 3.0% and 1.6% TRR (0.076 and 0.078 ppm) in low- and high-rate cranberries, respectively. Remaining radioactivity was simply characterized as "baseline" and accounted for ≤2.5% TRR.

Based on the cranberry metabolism study, the major metabolic pathway in cranberries involves cleavage of the cyclohexanedione ring to yield MNBA, which is further reduced to its amino analog, AMBA. HED notes that the proposed pathway is similar to that observed in field corn following treatment with PH-labeled mesotrione (Memo, S. Levy, 06-JUN-2001; DP#: 245477).

STUDY/WAIVER ACCEPTABILITY/DEFICIENCIES/CLARIFICATIONS:

Under the conditions and parameters used in the study, the cranberry plant metabolism data are classified as scientifically acceptable. The acceptability of this study for regulatory purposes is addressed in the forthcoming U.S. EPA Residue Chemistry Summary Document [DP#: 326898].

COMPLIANCE:

Signed and dated Good Laboratory Practice (GLP), Quality Assurance and Data Confidentiality statements were provided. No deviations from regulatory requirements were reported which would have an impact on the validity of the study.

A. BACKGROUND INFORMATION

Mesotrione is a triketone herbicide which inhibits the enzyme *p*-hydroxyphenylpyruvate dioxygenase (HPPD), disrupting carotenoid biosynthesis. This process leads to the destruction of chlorophyll, resulting in a bleaching effect in susceptible plants. Mesotrione is intended for preemergence and postemergence use for selective control of annual broadleaf weeds. Mesotrione is currently registered for use on field, pop, and sweet corn.

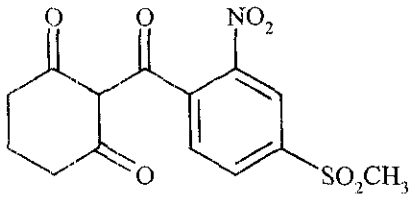
TABLE A.1. Mesotrione Nomenclature.	
Chemical structure	
Common name	Mesotrione
Company experimental name	ZA1296
IUPAC name	2-(4-mesyl-2-nitrobenzoyl)cyclohexane-1,3-dione
CAS name	2-[4-(methylsulfonyl)-2-nitrobenzoyl]-1,3-cyclohexanedione
CAS registry number	104206-82-8
End-use product (EP)	4 lb/gal flowable concentrate (FlC; Callisto® Herbicide; EPA Reg. No. 100-1131)

TABLE A.2. Physicochemical Properties of Mesotrione.		
Parameter	Value	Reference
Melting range	148.7-152.5°C	Memo, H. Podall, 24-FEB-2000; DP#: 263245
pH	3.4 (1% dispersion in water; 25°C)	
Density	1.46 g/mL, 20°C	
Water solubility	20°C 160 ppm, unbuffered water 0.22 g/100 mL, pH 4.8 1.5 g/100mL, pH 6.9 2.2 g/100 mL, pH 9	
Solvent solubility	20°C 0.37 g/100 mL, methanol 1.7 g/100 mL, ethyl acetate 0.27 g/100 mL, toluene 10.4 g/100 mL, acetonitrile <0.03 g/100 mL, heptane 8.1 g/100 mL, acetone	
Vapor pressure	4.3×10^{-8} torr, 20°C	
Dissociation constant, pK_a	3.12, 20 °C	
Octanol/water partition coefficient, Log(K_{OW})	20 ° C log P_{OW} = 0.11 in unbuffered water log P_{OW} = 0.90 in pH 5 buffer log P_{OW} <-1 at pH 7 and 9 buffered water	
UV/visible absorption spectrum	Absorption maximum in methanol at 256 mu, with a molar extinction coefficient of 2.24 x 104 M cm.	

B. EXPERIMENTAL DESIGN

B.1. Trial Site and Crop Information

Cranberry plants were grown in pots (30 plants for the low rate treatment and 10 plants for the high rate treatment) in separate cubicles by treatment in a greenhouse located at Syngenta Crop Protection (Greensboro, NC). The plants were pollinated by bumblebees for ~26 days after transplanting prior to application of the test substances. Temperatures were maintained between 21 and 27°C, and no supplemental lighting was used. Plants were watered automatically every other day for 2 minutes. The petitioner stated that the plants were grown according to normal agricultural practices; no maintenance pesticides were applied.

TABLE B.1.1. Trial Site Information.

Type	Method	Soil characteristics[1]			
		Type	%OM	pH	CEC
Foliar Treatment	Two applications with each test substance at each rate were made to bearing cranberry plants at a 16-day retreatment interval (RTI).	Sandy loam	84.4	4.0	34.3 meq/100 g

[1] OM = organic matter; CEC = cation-exchange capacity.

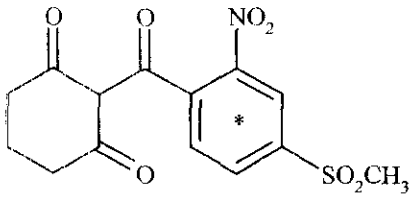
TABLE B.1.2. *Crop Information.*

Crop; crop group	Variety	Growth stage at application	Growth stage at harvest	Harvested Matrix
Cranberry (no crop group)	Howe (fruiting greenhouse variety)	Berries present	Maturity	Cranberries and foliage

B.2. Test Materials

The radiolabeled test substances were solubilized in ACN, then formulated as flowable concentrate formulations by diluting with formulation blank in water. The test material characteristics are presented in Table B.2.1.

TABLE B.2.1. Test Material Characteristics.

Chemical structure		
Radiolabel position	[phenyl-U-^{14}C]mesotrione	
Treatment	*Low rate*	High rate
Lot No.	BPM-XXVIII-43-1	BPM-XXVIII-73
Purity	98.2%	98%
Specific activity	40.8 µCi/mg (1.50 MBq/mg)	21.1 µCi/mg (0.77 MBq/mg)

B.3. Study Use Pattern

The formulated test substances were pipetted into scintillation vials containing water (1 vial/plant). Each vial was individually mixed and sprayed onto a cranberry plant. Two broadcast foliar applications were made for each treatment at rates of 0.30 and 0.22 lb ai/A for the low rate treatment, and 0.82 and 0.57 lb ai/A for the high rate treatment. The study use pattern is summarized in Table B.3.1.

TABLE B.3.1. Use Pattern Information.

Chemical name	[phenyl-U-^{14}C]mesotrione
Application method	Test substances solubilized with ACN and formulated as FlC formulations. Applied to plants as broadcast foliar sprays using a spray atomizer and low pressure air.
Application rate	Low rate: 0.30 lb ai/A (331 g ai/ha) + 0.22 lb ai/A (242 g ai/ha) for a total application rate of 0.52 lb ai/A High rate: 0.82 lb ai/A (919 g ai/ha) + 0.57 lb ai/A (642 g ai/ha) for a total application rate of 1.39 lb ai/A
Number of applications	2
Timing of applications	First applications: 33 days post-transplant Second applications: 49 days post-transplant (16-day RTI)
Pre-harvest interval (PHI)	46 days

B.4. Identification/Characterization of Residues

B.4.1. Sample Handling and Preparation

Samples of mature cranberries and foliage from both treatments were harvested by hand 46 days after the second application, and were placed in the greenhouse freezer (freezer temperatures not reported). Samples were shipped frozen to the first analytical facility (Syngenta Vero Beach Research Center, VBRC; Vero Beach, FL) within 2 days of harvest. At VBRC, samples were stored frozen (-20 to 5°C). Samples were processed by homogenization in the presence of dry ice, then radioassayed. Processed samples were shipped on dry ice via FedEx to Syngenta Crop Protection (Greensboro, NC) within 23 days of harvest for metabolite characterization and identification. At Greensboro, samples were stored frozen (~-20°C), and extracts were either stored frozen or refrigerated (~4°C).

Samples of cranberries were extracted 2-3x with ACN:water (4:1, v:v), then filtered. The extracts were combined, concentrated, and reserved for preparative HPLC analysis. The petitioner noted that a second subsample of low-rate cranberries was extracted later in the study using the same procedures because the original extract had been depleted.

Following preparative HPLC, Peaks 2 and 3 were isolated, combined, and subjected to acid hydrolysis with 1 N HCl at reflux for 4 hours; the resulting hydrolysate was neutralized with ammonium hydroxide and reserved for HPLC analysis.

B.4.2. Analytical Methodology

TRR in duplicate or triplicate aliquots of samples and nonextractable residues were determined by combustion/LSC; TRR in extracts were determined directly by LSC. The reported LOQs for TRR determinations were 0.004 ppm for the low-rate samples and 0.008 ppm for the high-rate samples.

Residues were isolated, identified, and quantitated in the ACN/water extracts of cranberries by HPLC analysis. HPLC analyses were conducted on a system equipped with a C18 column, variable-wavelength UV detector, radioisotope flow monitor (β-Ram detector), and fraction collector. A linear-gradient mobile phase of methanol/0.05% formic acid in water/ACN was used. Identification of mesotrione and its metabolites was confirmed by two-dimensional TLC. TLC analyses were conducted using silica-gel F-254 plates and solvent systems of chloroform:methanol:water (10:5:1, v:v:v) and ethyl acetate:methanol:water:acetic acid (83:10:5:2, v:v:v:v). Radioactivity was detected by radioanalytic imaging, and nonradiolabeled standards were detected by UV light (254 nm). Mesotrione and metabolites MNBA and AMBA were identified by co-chromatography comparisons with nonlabeled and radiolabeled reference standards. Chemical names and structures for the reference standards are presented in Appendix I.

Identification of mesotrione was also confirmed by LC/MS/MS conducted on a system equipped with a triple-quadrupole mass spectrometer with electrospray ionization or atmospheric-pressure chemical ionization (APCI), and a radioisotope flow monitor.

C. RESULTS AND DISCUSSION

The storage conditions and intervals for cranberries are presented in Table C.1. The petitioner provided critical sample handling and storage dates for all samples. Initial profiling was completed within 35-36 days of harvest. A second subsample of low-rate cranberries was extracted 5 months after harvest for further characterization of residues, and analysis of this extract was completed within 161-340 days (5.3-11.2 months) of harvest; the extract from the second extraction was stored for up to 6 months. To support storage conditions and intervals of samples, the petitioner re-extracted and analyzed samples of low-rate cranberries 375 days (12.3 months) after harvest (extract stored for 58 days), and compared the results with those of low rate cranberries from initial profiling. When extractability of residues into ACN/water and distribution of individual peaks on HPLC analysis were compared, no significant differences in either factor were observed following extended storage. The submitted storage stability data are adequate to support the cranberry metabolism study. Although no storage stability data were submitted to support the 6-month storage interval for the second-extraction extract, because initial profiling, characterization, and metabolite isolation was completed using the first-extraction extract, and quantitative recovery of the TRR as identified metabolites was high in low rate cranberries, no additional data are required.

Samples of cranberries and foliage were collected 46 days after two foliar applications of PH-labeled mesotrione at 0.30 and 0.22 lb ai/A for a total application rate of 0.52 lb ai/A (low rate), or 0.82 and 0.57 lb ai/A for a total application rate of 1.39 lb ai/A (high rate).

TRR in cranberry matrices were determined by combustion/LSC; TRR are reported in Table C.2.1. TRR were 2.573 ppm in cranberries and 16.832 ppm in foliage collected 46 days following the low-rate application, and 4.853 ppm in cranberries and 31.804 ppm in foliage collected 46 days following the high-rate application. Only cranberries were subjected to analysis for residue characterization and identification.

The distribution of the radioactivity in cranberries is presented in Table C.2.2. Solvent extraction with ACN/water released a reported ~103% TRR in low-rate cranberries and ~102% TRR in high-rate cranberries. Nonextractable residues accounted for 2.5% TRR (0.064 ppm) in low-rate cranberries and 2.2% TRR (0.107 ppm) in high-rate cranberries. Accountabilities were 104-105%. The extraction procedures were adequate. Residues were identified and quantitated by HPLC, and identification of metabolites was confirmed by TLC co-chromatography and by LC/MS/MS (mesotrione only).

The characterization and identification of residues in cranberries is summarized in Table C.2.3. Mesotrione was the major residue identified in cranberries, accounting for 60.2% TRR (1.548 ppm) in low-rate cranberries and for 67.1% TRR (3.257 ppm) in high rate cranberries. The metabolite AMBA was also a significant component, accounting for 34.8% TRR (0.895 ppm) in low-rate cranberries and for 24.3% TRR (1.178 ppm) in high-rate cranberries. Metabolite MNBA was identified at 3.0% and 1.6% TRR (0.076 and 0.078 ppm) in low- and high-rate cranberries, respectively. Remaining radioactivity was simply characterized as "baseline" and accounted for ≤2.5% TRR.

HPLC analysis of the ACN/water extract yielded discrete peaks for mesotrione (Peak 4) and MNBA (Peak 1); however, AMBA appeared as a broad region comprising two peaks (Peaks 2 and 3). To confirm identification of AMBA, the combined peaks were subjected to acid hydrolysis, identification was confirmed by HPLC and TLC co-chromatography of the resulting hydrolysate.

C.1. Storage Stability

Samples of cranberries were stored frozen (~-20°C) prior to HPLC profiling and analysis. The petitioner provided critical sample handling and storage dates for all samples. Initial profiling was completed within 35-36 days of harvest. A second subsample of low rate cranberries was extracted 5 months after harvest for further characterization of residues, and analysis of this extract was completed within 161-340 days (5.3-11.2 months) of harvest; the extract from the second extraction was stored for up to 6 months.

To support storage conditions and intervals of samples, the petitioner re-extracted and analyzed samples of low rate cranberries 375 days (12.3 months) after harvest (extract stored for 58 days), and compared the results with those of low rate cranberries from initial profiling. When

extractability of residues into ACN/water and distribution of individual peaks on HPLC analysis were compared, no significant differences in any of the factors were observed following extended storage.

The submitted storage stability data are adequate to support the cranberry metabolism study. Although no storage stability data were submitted to support the 6-month storage interval for the second-extraction extract, because initial profiling, characterization, and metabolite isolation was completed using the first-extraction extract, and quantitative recovery of the TRR as identified metabolites was high in low-rate cranberries, no additional data are required.

TABLE C.1. Summary of Storage Conditions.

Matrix[1]		Storage Temperature (°C)	Actual Storage Duration[2]	Interval of Demonstrated Storage Stability
Cranberry – first extraction; both rates		~-20	35-36 days	375 days (12.3 months)
Cranberry – second extraction; low rate	RAC	~-20	161-340 days (5.3-11.2 months)	375 days (12.3 months)
	Extract	~-20	3-182 days (0.1-6.0 months)	58 days (1.9 months)

[1] Extracts were stored for 6 days, except where noted.
[2] Interval from harvest to analysis.

C.2. Identification, Characterization, and Distribution of Residues

TABLE C.2.1. TRR in Cranberry Matrices.

Matrix	Timing and Applic. No.	PHI (days)	TRR, ppm	
			0.52 lb ai/A	1.39 lb ai/A
Cranberries	Two foliar	46	2.573	4.853
Foliage			16.823	31.804

TABLE C.2.2. Distribution of the Parent and the Metabolites in Cranberries Following Application of [Phenyl-U-^{14}C]Mesotrione at 0.52 and 1.39 lb ai/A.[1]

Metabolite Fraction	0.52 lb ai/A		1.39 lb ai/A	
	TRR = 2.573 ppm		TRR = 4.853 ppm	
	%TRR	ppm	%TRR	ppm
First extraction				
ACN/water	102.5	2.637	101.7	4.936
Mesotrione	60.2	1.548	67.1	3.257
MNBA	3.0	0.076	1.6	0.078
AMBA[2]	34.8	0.895	24.3	1.178
Baseline	1.6	0.042	1.2	0.057
Nonextractable	2.5	0.064	2.2	0.107
Second extraction[3]				
ACN/water	105.1	2.704		
Nonextractable	4.8	0.124		

[1] Shading indicates that the extraction step and/or characterization analysis was not conducted for the matrix in question.
[2] Identified after peak isolation and acid hydrolysis.
[3] No details were provided concerning characterization of residues in this extract.

TABLE C.2.3. Summary of Characterization and Identification of Radioactive Residues in Cranberries Following Application of [Phenyl-U-^{14}C]Mesotrione at 0.52 and 1.39 lb ai/A.

Compound	0.52 lb ai/A		1.39 lb ai/A	
	TRR = 2.573 ppm		TRR = 4.853 ppm	
	% TRR	ppm	% TRR	ppm
Mesotrione	60.2	1.548	67.1	3.257
MNBA	3.0	0.076	1.6	0.078
AMBA[1]	34.8	0.895	24.3	1.178
Baseline	1.6	0.042	1.2	0.057
Total identified	98.0	2.519	93.0	4.513
Total characterized	1.6	0.042	1.2	0.057
Total extractable	102.5	2.637	101.7	4.936
Unextractable (PES)[2]	2.5	0.064	2.2	0.107
Accountability[3]	105		104	

[1] Identified after peak isolation and acid hydrolysis.
[2] Residues remaining after exhaustive extractions.
[3] Accountability = (Total extractable + Total unextractable)/(TRR from combustion analysis; see TABLE C.2.1) * 100.

C.3. Proposed Metabolic Profile

Based on the cranberry metabolism study, the major metabolic pathway in cranberries involves cleavage of the cyclohexanedione ring to yield MNBA, which is further reduced to its amino analog, AMBA.

FIGURE C.3.1. Proposed Metabolic Profile of PH-Labeled Mesotrione in Cranberry

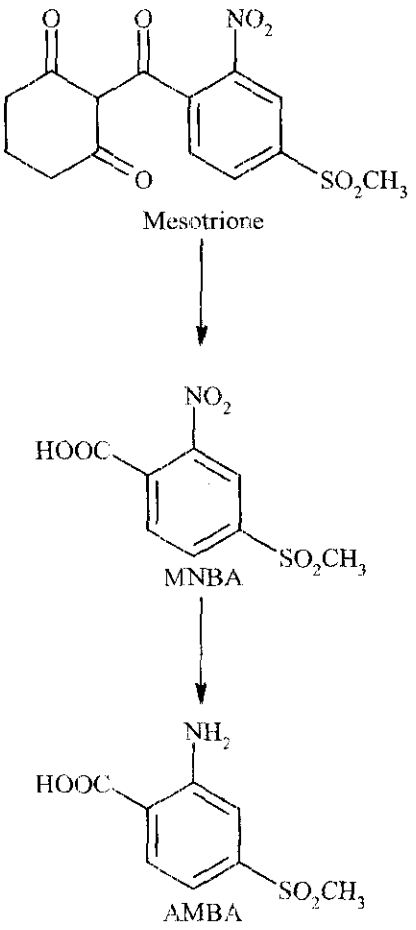
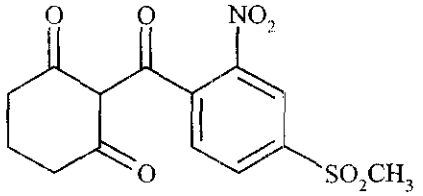
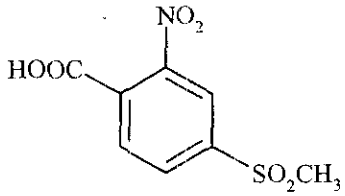
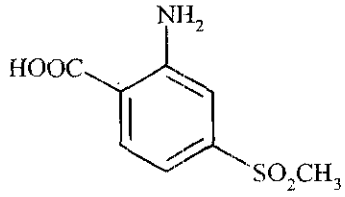


TABLE C.3.1. Identification of Compounds from Metabolism Study.

Common name/code Figure C.3.1 ID No.	Chemical name	Chemical structure
Mesotrione ZA1296	2-[4-(methylsulfonyl)-2-nitrobenzoyl]-1,3-cyclohexanedione	
MNBA	4-methanesulfonyl-2-nitro-benzoic acid	
AMBA	2-amino-4-methanesulfonyl-benzoic acid	

D. CONCLUSION

Following two broadcast foliar applications of PH-labeled mesotrione to cranberries 33 and 49 days post-transplant at 0.30 and 0.22 lb ai/A for a total application rate of 0.52 lb ai/A (low rate), or 0.82 and 0.57 lb ai/A for a total application rate of 1.39 lb ai/A (high rate), TRR were 2.573 ppm in cranberries and 16.832 ppm in foliage collected 46 days following the low-rate application, and 4.853 ppm in cranberries and 31.804 ppm in foliage collected 46 days following the high-rate application.

Solvent extraction with ACN/water released a reported ~103% TRR in low-rate cranberries and ~102% TRR in high-rate cranberries. Nonextractable residues accounted for 2.5% TRR (0.064 ppm) in low rate cranberries and 2.2% TRR (0.107 ppm) in high-rate cranberries. The extraction procedures were adequate, and adequate storage stability data were submitted to support the storage intervals and conditions of samples from the study.

Mesotrione was the major residue identified in cranberries, accounting for 60.2% TRR in low rate cranberries and for 67.1% TRR in high rate cranberries. The metabolite AMBA, identified after peak isolation and acid hydrolysis, was also a significant component, accounting for 34.8% TRR in low rate cranberries and for 24.3% TRR in high rate cranberries. Metabolite MNBA was also identified at 3.0% and 1.6% TRR in low- and high-rate cranberries, respectively. Remaining radioactivity was simply characterized as "baseline" and accounted for ≤2.5% TRR.

E. REFERENCES

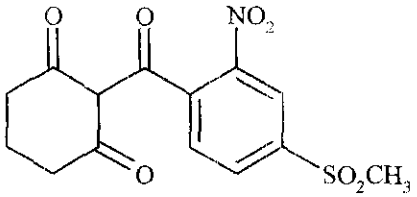
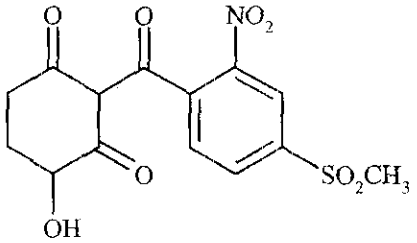
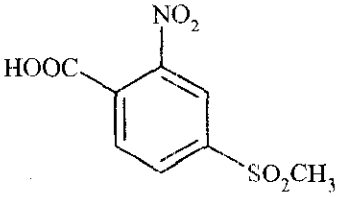
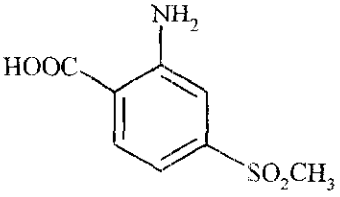
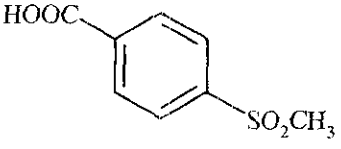
DP#s: 245477 and 260267
Subject: PP#: 8F04954. Mesotrione in/on Field Corn. Evaluation of Residue Data and Analytical Methods. PC Code: 122990. Case #: 289589. Submission #s: S541377 and S569871.
From: S. Levy
To: J. Stone /J. Tompkins
Date: 06-JUN-2001
MRIDs: 44505118, 44505212-23, 44537109-12, 44901719, and 44942401-03

F. DOCUMENT TRACKING

RDI: G.F. Kramer (02-MAR-2007), RAB1 Chemists (08-NOV-2006)
S. Levy:S10953:PY1:(703)305-0783:7509P:RAB1
Petition#: 6F7023
DP#: 326898
PC Code: 122990

Template Version June 2005

APPENDIX I. Chemical Names and Structures of Reference Standards Used in Cranberry Metabolism Study.

Common name; Company code	Chemical name	Chemical structure
Mesotrione[1] ZA1296	2-[4-(methylsulfonyl)-2-nitrobenzoyl]-1,3-cyclohexanedione	
4-hydroxy-mesotrione R282813	4-hydroxy-2-[4-(methylsulfonyl)-2-nitrobenzoyl]-1,3-cyclohexanedione	
MNBA [1]	4-methanesulfonyl-2-nitro-benzoic acid	
AMBA [1]	2-amino-4-methanesulfonyl-benzoic acid	
MBA	4-methanesulfonyl-benzoic acid	

[1] Both radiolabeled and nonlabeled standards were used.

Mesotrione/ZA1296/PC Code 122990/ Interregional Research Project No. 4 (IR-4)
DACO 7.4.1/7.4.2/OPPTS 860.1500/OECD IIA 6.3.1, 6.3.2, 6.3.3 and IIIA 8.3.1, 8.3.2, 8.3.3
Crop Field Trial - Cranberry

Primary Evaluator: Sarah J. Levy, Chemist
Registration Action Branch (RAB1)
Health Effects Division (HED) (7509P)
Date: 02-MAR-2007

Approved by: George F. Kramer, Ph.D., Senior Chemist
RAB1/HED (7509P)
Date: 02-MAR-2007

This data-evaluation record (DER) was originally prepared under contract by Dynamac Corporation (2275 Research Boulevard, Suite 300; Rockville, MD 20850; submitted 29-SEP-2006). The DER has been reviewed by the HED and revised to reflect current Office of Pesticide Programs (OPP) policies.

STUDY REPORT:

46726307 Salzman, F. (2005) Mesotrione: Magnitude of the Residue on Cranberry. Project Number: 08903. Unpublished study prepared by Interregional Research Project No. 4, IR-4 Western Region Analytical Lab. and Agricultural Chemicals Development Services, Inc. 142 p.

EXECUTIVE SUMMARY:

The Interregional Research Project No. 4 (IR-4) has submitted field trial data for mesotrione on cranberry. Five trials were conducted in Regions 1 (MA; 1 trial), 2 (NJ; 1 trial), 5 (WI; 2 trials), and 12 (OR; 1 trial) during the 2004 growing season.

At each trial location, two foliar broadcast applications of a 4 pound per gallon (lb/gal) flowable concentrate (FlC) mesotrione formulation were made at ~0.3 lbs active ingredient per acre (ai/A) for the first application and ~0.2 lb ai/A for the second application, for a total application rate of ~0.5 lb ai/A. Applications were made at 13- to 15-day retreatment intervals (RTIs) using ground equipment in spray volumes of 20-29 gal/A. A nonionic surfactant was added to the spray mixtures at all trials except the OR trial, where an insecticidal petroleum oil concentrate was inadvertently used instead of a crop-oil concentrate (COC) as the spray adjuvant. Mature cranberries were harvested 43-48 days after the last application.

Samples of cranberries were analyzed for residues of mesotrione *per se* using a modified version of liquid chromatography (LC)/mass spectroscopy (MS)/MS method RAM 366/01. This method was previously reviewed and forwarded to the U.S. Food and Drug Administration (FDA) for inclusion in Pesticide Analytical Manual (PAM) Volume II as a confirmatory enforcement method for plant commodities (Memo, W. Cutchin, 12-JAN-2005; DP#: 283827). The lowest level of method validation (LLMV) was 0.01 ppm. Based on recoveries at the LLMV, the calculated limit of quantitation (LOQ) and limit of detection (LOD) were 0.015 ppm and 0.005 ppm, respectively, for cranberry. This method is adequate for data collection based on acceptable method validation and concurrent recovery data. HED notes that, although the petitioner used the LLMV of 0.01 ppm as the quantitation limit for reporting residue results, based on the calculated LOQ, the method does not reliably quantitate residues down to 0.01 ppm.

The maximum storage interval of cranberry samples from harvest to analysis was 238 days (7.8 months). Storage stability data generated concurrently with the field trials indicate that residues of mesotrione are stable in fortified samples of cranberry stored frozen for up to 217 days (7.1 months).

Residues of mesotrione were reported as <0.01 ppm in/on all cranberry samples harvested 43-48 days following foliar treatments with the 4 lb/gal FlC formulation at total seasonal rates of 0.503-0.560 lb ai/A. Residue decline data were not submitted.

STUDY/WAIVER ACCEPTABILITY/DEFICIENCIES/CLARIFICATIONS:

Under the conditions and parameters used in the study, the field trial residue data are classified as scientifically acceptable. The acceptability of this study for regulatory purposes is addressed in the forthcoming U.S. EPA Residue Chemistry Summary Document [DP#: 326898].

COMPLIANCE:

Signed and dated Good Laboratory Practice (GLP), Quality Assurance and Data Confidentiality statements were provided. No deviations from regulatory requirements were reported which would have an impact on the validity of the study.

A. BACKGROUND INFORMATION

Mesotrione is a triketone herbicide which inhibits the enzyme *p*-hydroxyphenylpyruvate dioxygenase (HPPD), disrupting carotenoid biosynthesis. This process leads to the destruction of chlorophyll, resulting in a bleaching effect in susceptible plants. Mesotrione is intended for preemergence and postemergence use for selective control of annual broadleaf weeds. Mesotrione is currently registered for use on field, pop, and sweet corn.

TABLE A.1. Mesotrione Nomenclature.

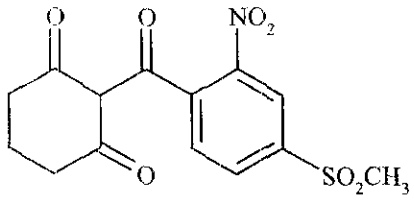
Chemical structure	
Common name	Mesotrione
Company experimental name	ZA1296
IUPAC name	2-(4-mesyl-2-nitrobenzoyl)cyclohexane-1,3-dione
CAS name	2-[4-(methylsulfonyl)-2-nitrobenzoyl]-1,3-cyclohexanedione
CAS registry number	104206-82-8
End-use product (EP)	4 lb/gal FlC (Callisto® Herbicide; EPA Reg. No. 100-1131)

TABLE A.2. Physicochemical Properties of Mesotrione.		
Parameter	Value	Reference
Melting point/range	148.7-152.5°C	RD Memo, H. Podall, 24-FEB-2000; DP#: 263245.
pH	3.4 (1% dispersion in water; 25°C)	
Density	1.46 g/mL, 20°C	
Water solubility	20°C *160 ppm, unbuffered water* 0.22 g/100 mL, pH 4.8 1.5 g/100mL, pH 6.9 2.2 g/100 mL, pH 9	
Solvent solubility	20°C 0.37 g/100 mL, methanol 1.7 g/100 mL, ethyl acetate 0.27 g/100 mL, toluene 10.4 g/100 mL, acetonitrile <0.03 g/100 mL, heptane 8.1 g/100 mL, acetone	
Vapor pressure	4.3×10^{-8} torr, 20°C	
Dissociation constant, pK_a	3.12, 20°C	
Octanol/water partition coefficient, Log(K_{OW})	20°C log P_{OW} = 0.11 in unbuffered water log P_{OW} = 0.90 in pH 5 buffer log P_{OW} <-1 at pH 7 and 9 buffered water	
UV/visible absorption spectrum	Absorption maximum in methanol at 256 mu, with a molar extinction coefficient of 2.24 x 104 M cm.	

B. EXPERIMENTAL DESIGN

Five cranberry trials were conducted in Regions 1 (MA; 1 trial), 2 (NJ; 1 trial), 5 (WI; 2 trials), and 12 (OR; 1 trial) during the 2004 growing season.

Each field trial consisted of one untreated plot and one treated plot. The study use pattern is presented in Table B.1.2. At each trial, two foliar broadcast applications of a 4 lb/gal FlC formulation of mesotrione were made at ~0.3 lb ai/A for the first application and ~0.2 lb ai/A for the second application, for a total rate of ~0.5 lb ai/A. At one trial (OR), the boom hose became caught on an irrigation riser within the first 3 feet of the first pass in the first application; however, only half of the plot was affected. The petitioner noted that cranberries were harvested only from the second half of the plot, and that on the second half mesotrione was over-applied by 15%. Applications were made at 13- to 15-day RTIs using ground equipment (CO_2 backpack sprayer) in spray volumes of 20-29 gal/A. A nonionic surfactant was added to the spray mixtures at all trials except the OR trial, where an insecticidal petroleum oil concentrate was inadvertently used instead of a COC as the spray adjuvant.

Common cultural practices were followed, and maintenance pesticides and fertilizers were used to produce a commercial quality crop. Trial site conditions are presented in Table B.1.1. The crop varieties grown are identified in Table C.3. The petitioner included the overall monthly rainfall and temperature ranges for each trial site and stated that actual temperatures were outside

the average historical ranges at all trial sites. Rainfall amounts were below the average historical values, except in September at the OR trial (where rainfall was higher than the average). Irrigation was used to supplement rainfall as needed at all trial sites. The following weather conditions were noted: at the MA trial temperatures were below normal (≤30°F) during the growing season, and August was cloudy and wet; and at the NJ trial rainfall amounts were above normal in July and September, and temperatures were below normal during August and September. No phytotoxic effects were observed in the trials due to pesticide application.

B.1. Study Site Information

TABLE B.1.1. Trial Site Conditions.

Trial Identification: City, State; Year (Trial No.)	Soil characteristics[1]			
	Type	%OM	pH	CEC (meq/100 g)
Tabernacle, NJ; 2004 (04-NJ26)	sand	2.9	4.3	1.4
East Wareham, MA; 2004 (04-MA01)	sand	1.4	4.9	2.8
Warrens, WI; 2004 (04-WI18)	sand	6.7	4.9	Not reported (NR)
Warrens, WI; 2004 (04-WI19)	sand	7	5.9	NR
Bandon, OR; 2004 (04-OR18)	artificial soil (layers of peat, beach sand, and duff)	NR	NR	NR

[1] OM = organic matter; CEC = cation-exchange capacity.

TABLE B.1.2. Study Use Pattern.

Location: City, State; Year (Trial ID)	EP[1]	Application					Tank Mix/ Adjuvants
		Method; Timing	Volume (gal/A)	Rate (lb ai/A)	RTI[2] (days)	Total Rate (lb ai/A)	
Tabernacle, NJ; 2004 (04-NJ26)	4 lb/gal FlC	1. Foliar broadcast; fruiting	23.70	0.3084	--	0.5096	NIS (0.2%, v:v)
		2. Foliar broadcast; fruiting	23.16	0.2012	15		
East Wareham, MA; 2004 (04-MA01)	4 lb/gal FlC	1. Foliar broadcast; fruit development	20.31	0.3042	--	0.5040	NIS (0.2%, v:v)
		2. Foliar broadcast; fruit sizing, early color	20.44	0.1998	13		
Warrens, WI; 2004 (04-WI18)	4 lb/gal FlC	1. Foliar broadcast; fruiting	26.14	0.3064	--	0.5026	NIS (0.2%, v:v)
		2. Foliar broadcast; fruiting	24.83	0.1962	13		
Warrens, WI; 2004 (04-WI19)	4 lb/gal FlC	1. Foliar broadcast; fruiting	26.72	0.3156	--	0.5123	NIS (0.2%, v:v)
		2. Foliar broadcast; fruiting	24.65	0.1967	13		
Bandon, OR; 2004 (04-OR18)	4 lb/gal FlC	1. Foliar broadcast; small under-ripe berries	29.12	0.3458	--	0.5601	insecticidal petroleum oil concentrate[3] (1%, v:v)
		2. Foliar broadcast; fruit white and pink	27.74	0.2143	15		

[1] EP = End-use product; 4SC-A; Callisto® Herbicide (EPA Reg. No. 100-1131).
[2] *RTI = Retreatment interval*
[3] The petroleum oil concentrate (Omni Supreme Spray®) was believed by the field director to be a COC.

TABLE B.1.3. Trial Numbers and Geographical Locations.

NAFTA Growing Regions	Cranberry		
	Submitted	Requested	
		Canada	U.S.
1	1		2
2	1		
5	2		2
12	1		1
Total	5		5

B.2. Sample Handling and Preparation

Duplicate control and treated samples (≥2 lbs each) of mature cranberries were harvested by hand (cranberry scoop or rake) from each site 43-48 days after the last application. Vines, stems and leaves were removed by hand. All samples were placed in frozen storage at the field sites within approximately 5 hours of collection and were shipped frozen to Del Monte Research Center (Walnut Creek, CA), where samples were ground with dry ice and maintained frozen (<-10°C). Prepared samples were then transferred to the IR-4 Western Region Laboratory (Davis, CA) for residue analysis. Samples were stored frozen (<-20°C) at the analytical laboratory until extraction and analysis.

B.3. Analytical Methodology

Samples of cranberry were analyzed for residues of mesotrione using LC/MS/MS method, RAM 366/01, entitled "Residue Analytical Method for the Determination of Residues of Mesotrione and 4-(Methylsufonyl)-2-Nitrobenzoic Acid (MNBA) in Crop Samples." A detailed description of the method was included in the STUDY REPORT. This method has been previously reviewed and was forwarded to FDA for inclusion in PAM Vol. II as a confirmatory enforcement method for plant commodities (Memo, W. Cutchin, 12-JAN-2005; DP#: 283827). Minor modifications to the method were made for the analysis of cranberry (*i.e.*, samples were not analyzed for MNBA (4-methanesulfonyl-2-nitro-benzoic acid); a methylene chloride partitioning step was added to remove pigments; and standards and samples were diluted with acetonitrile (ACN)/water to reflect the mobile phase).

Briefly, homogenized samples are extracted with ACN:water containing 10 g/L sodium chloride (1:1, v:v) and centrifuged. An aliquot of the extract was diluted with water and formic acid, and cleaned up by solid-phase extraction (SPE) on a polymeric column; residues were eluted with methanol:formic acid (98:2, v:v). The eluate was diluted with water and partitioned into methylene chloride. The methylene chloride phase was evaporated to dryness, and residues were redissolved in ACN/water (10%, v:v) for LC/MS/MS analysis. The monitored ion transition was m/z 338 → 291. The LLMV was 0.01 ppm. Based on recoveries at the LLMV, the calculated LOQ and LOD were 0.015 ppm and 0.005 ppm, respectively, for cranberry; the petitioner used the LLMV as the quantitation limit for reporting residue results.

The method was validated prior to and concurrently with the analysis of field trial samples using control samples of cranberries fortified with mesotrione at 0.01-1.0 ppm.

A concurrent storage stability study was conducted using untreated cranberry samples fortified with mesotrione, and stored frozen for the duration of the field trial study. No 0-day data were generated to demonstrate initial residue levels.

C. RESULTS AND DISCUSSION

Sample storage conditions and intervals are summarized in Table C.2.1. The maximum storage interval of cranberry samples from harvest to analysis was 238 days (7.8 months). To support the storage interval for cranberry samples, a concurrent storage stability study was conducted. The results of the storage stability study are presented in Table C.2.2. Although 0-day data were not provided, the storage stability data indicate that residues of mesotrione are relatively stable in/on fortified samples of cranberry stored frozen up to 217 days.

Method validation and concurrent recovery data are presented in Table C.1. Samples of cranberries were analyzed for residues of mesotrione *per se* using a modified version of HPLC/MS/MS method RAM 366/01. This method was previously reviewed and forwarded to FDA for inclusion in PAM Vol. II as a confirmatory enforcement method for plant commodities (Memo, W. Cutchin, 12-JAN-2005; DP#: 283827). The LLMV was 0.01 ppm. Based on recoveries at the LLMV, the calculated LOQ and LOD were 0.015 ppm and 0.005 ppm, respectively, for cranberry. Adequate sample calculations and chromatograms were provided. Apparent residues of mesotrione were <0.010 ppm in/on five samples of untreated cranberries.

This method is adequate for data collection based on acceptable method validation and concurrent recovery data. Method validation recoveries ranged 70-117% (mean = 102%) for samples fortified at 0.010, 0.10, and 1.00 ppm. Concurrent recoveries were 81% and 102% for samples fortified at 0.10 ppm. Although no concurrent recovery data were obtained reflecting fortification at 0.01 ppm, acceptable recoveries at 0.01 ppm were obtained during both method validation and concurrent recovery analyses conducted within 3-4 days of sample analysis. HED notes that, although the petitioner used the LLMV of 0.01 ppm as the quantitation limit for reporting residue results, based on the calculated LOQ, the method does not reliably quantitate residues down to 0.01 ppm.

Residue data from the cranberry field trials are reported in Table C.3. A summary of the residue data for cranberries is presented in Table C.4. Residues of mesotrione were reported as <0.01 ppm in/on all cranberry samples harvested 43-48 days following the last of two foliar broadcast spray applications of the 4 lb/gal FlC formulation at total seasonal rates of 0.503-0.560 lb ai/A.

Residue decline data were not submitted and are not required to support the 43-48-day PHI reflected in the field trials.

TABLE C.1. Summary of Method Validation and Concurrent Recoveries of Mesotrione from Cranberry.

Matrix	Spike level (ppm)	Sample size (n)	Recoveries (%)	Mean ± std dev (%)
Method Validation				
Cranberry	0.010	6	70, 86, 95, 103, 121, 124	100 ± 21
	0.10	3	92, 99, 106	99 ± 7
	1.00	3	94, 115, 117	109 ± 13
Concurrent Validation				
Cranberry	0.10	2	81, 102	92

[1] Fresh fortification recoveries from the concurrent storage stability study (see Table C.2.2).

TABLE C.2.1. Summary of Storage Conditions.

Matrix	Storage Temperature (°C)	Actual Storage Duration[1]	Interval of Demonstrated Storage Stability
Cranberry	<-10	230-238 days (7.6-7.8 months)	Residues of mesotrione are relatively stable in/on cranberry stored frozen for up to 217 days.[2]

[1] Interval from harvest to analysis. All samples were analyzed within 1 day of extraction.
[2] Storage stability data (refer to Table C.2.2) submitted in conjunction with the subject field trials.

TABLE C.2.2 Stability of Mesotrione in/on Cranberry Stored Frozen.

Matrix	Spike Level (ppm)	Storage interval (days)	Freshly Fortified Recovery (%) [Avg.]	Stored Sample Recovery (%) [Avg.]	Average Corrected Stored Recovery (%)[1]
Cranberry	0.010	217	106, 116, 116 [113]	97, 98, 106 [100]	88
	0.10		89, 94, 98 [94]	--	--

[1] Corrected for average recovery in freshly fortified samples.

TABLE C.3. Residue Data from Cranberry Crop Field Trials with Mesotrione.

Trial: City, State; Year (Trial ID)	Region	Crop Variety	Commodity or Matrix	Total Rate (lb ai/A)	PHI (days)	Mesotrione Residues (ppm)
Tabernacle, NJ; 2004 (04-NJ26)	1	Early Black	berry	0.5096	44	<0.01, <0.01
East Wareham, MA; 2004 (04-MA01)	2	Early Black	berry	0.5040	43	<0.01, <0.01
Warrens, WI; 2004 (04-WI18)	5	McFarlin	berry	0.5026	43	<0.01, <0.01
Warrens, WI; 2004 (04-WI19)	5	Stevens	berry	0.5123	43	<0.01, <0.01
Bandon, OR; 2004 (04-OR18)	12	McFarlin	berry	0.5601	48	<0.01, <0.01

TABLE C.4. Summary of Residue Data from Crop Field Trials with Mesotrione.

Commodity	Total Applic. Rate (lb ai/A)	PHI (days)	Residue Levels[1] (ppm)						
			n	Min.	Max.	HAFT[2]	Median	Mean	Std. Dev.
Cranberry	0.5026-0.5601	43-48	10	<0.015	<0.015	<0.015	<0.008	<0.008	0.0

[1] For calculation of the minimum, maximum, and HAFT, the calculated LOQ of 0.015 ppm was used for residues reported as <0.01 ppm in Table C.3; for calculation of the median, mean, and standard deviation, 0.008 ppm (half the calculated LOQ) was used for residues reported as <0.01 ppm.
[2] HAFT = Highest-Average Field Trial.

D. CONCLUSION

The IR-4 has submitted data from five field trials for mesotrione on cranberry during the 2004 growing season. At each trial location, two foliar broadcast applications of a 4 lb/gal FlC formulation were made at a total application rate of 0.503-0.560 lb ai/A. Applications were made at 13- to 15-day RTIs using ground equipment in spray volumes of 20-29 gal/A. A nonionic surfactant was added to the spray mixtures at all trials except the OR trial, where an insecticidal petroleum oil concentrate was inadvertently used instead of a COC as the spray adjuvant. Samples of mature cranberries were harvested at a 43- to 48-day PHI. Residues of mesotrione were reported as <0.01 ppm in/on all cranberry samples. Residue decline data were not submitted. An acceptable method was used for quantitation of residues in/on cranberries, and adequate data are available to support sample storage intervals and conditions.

E. REFERENCES

DP#: 263245
Subject: Product Chemistry Review of Mesotrione (ZA 1296 Technical (dry)).
From: H. Podall
To: J. Tompkins/J. Stone
Date: 24-FEB-2000
MRIDs: 44373503-44373505, 44505003, 44505004, and 44901701

DP#s: 245477 and 260267
Subject: PP#: 8F04954. Mesotrione in/on Field Corn. Evaluation of Residue Data and Analytical Methods. PC Code: 122990.
From: S. Levy
To: J. Stone/ J. Tompkins
Dated: 06-JUN-2001
MRIDs: 44505118, 44505212-23, 44537109-12, 44901719, and 44942401-03

DP#: 283827
Subject: Mesotrione. Summary of Analytical Chemistry and Residue Data for Sweet Corn, PP#2F06443, and Response to Data Deficiencies of a Previous HED Review (PP#8F04954, DP Barcodes: D245477 and D260267, 6/6/01, S. Levy).
From: W. Cutchin
To: J. Stone/ J. Miller
Dated: 12-JAN-2005
MRIDs: 45651801-45651803, 45651813, 45651814, 45651816, 45651817, and 45665901

F. DOCUMENT TRACKING

RDI: G.F. Kramer (02-MAR-2007), RAB1 Chemists (15-NOV-2006)
S. Levy:S10953:PY1:(703)305-0783:7509P:RAB1
Petition#: 6F7023
DP#: 326898
PC Code: 122990

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